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(71) Applicant (*for all designated States except US*): **JANSSEN PHARMACEUTICA N.V.** [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **FREYNE, Eddy, Jean, Edgard** [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). **LACRAMPE, Jean, Fernand, Armand** [FR/FR]; Johnson & Johnson Pharmaceutical, Research and Development, A Division of Janssen-Cilag Campus de Maigremont, BP 615, F-27106 Val de Reuil Cedex (FR). **PERERA, Timothy, Pietro, Suren** [GB/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). **TEN HOLTE, Peter** [NL/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). **LIGNY, Yannick, Aimé, Eddy** [FR/FR]; Johnson & Johnson Pharmaceutical, Research and Development, A Division of Janssen-Cilag Campus de Maigremont, BP 615, F-27106 Val de Reuil Cedex (FR). **LARDEAU, Delphine, Yvonne, Raymonde** [FR/FR]; Johnson & Johnson Pharmaceutical, Research and Development, A Division of Janssen-Cilag Campus de Maigremont, BP 615, F-27106 Val de Reuil Cedex (FR). **LAVRIJSSEN, Tom** [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE).

(74) Common Representative: **JANSSEN PHARMACEUTICA N.V.**; Turnhoutseweg 30, B-2340 Beerse (BE).

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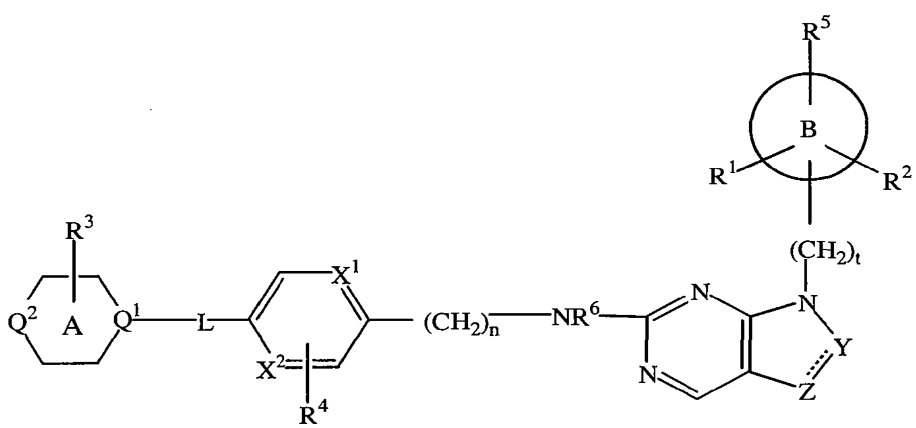
(54) **Title:** 5-MEMBERED ANNELATED HETEROCYCLIC PYRIMIDINES AS KINASE INHIBITORS



(I)

(57) **Abstract:** This invention comprises the novel compounds of formula (I) wherein R^1, R^2, R^3, R^4, R^5, R^6, Q^1, Q^2, X^1, X^2, Y and Z have defined meanings, having cell cycle kinase inhibiting enzymatic activity, their preparation, compositions containing them and their use as a medicine.

WO 2006/074985 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

5-MEMBERED ANNELATED HETEROCYCLIC PYRIMIDINES AS KINASE INHIBITORS

Field of the invention

The present invention relates to compounds and compositions containing said compounds acting as inhibitors of cell-cycle specific kinases, more in particular the cyclin dependent kinase CDK4 and/or the Aurora kinases AURORA A and/or AURORA B. Moreover, the present invention provides processes for the preparation of the disclosed inhibitors, and methods of using them, for instance as a medicine.

In normal cells the cell cycle is a tightly regulated and carefully balanced process through which one cell divides into two. The four phases, G1, S, G2 and M phase, reflect stages in cell cycle progression where DNA synthesis and replication (S phase) and mitosis (M phase) occur in a temporally regulated fashion, separated by two gap phases (G1 and G2). Cell cycle progression is maintained by an array of regulatory decision points, governed in part by cyclin dependent kinases (Cdks), which determine whether it is appropriate for a cell to divide. In addition to the catalytic subunit (the Cdk itself), each Cdk complex contains one of many activating subunits called cyclins because their levels fluctuate periodically throughout the cell cycle. Distinct cyclin-Cdk complexes power the cell through different phases of the cell cycle. In mammals, these complexes include the D-type cyclins which activate Cdk4 to execute critical regulatory events in G1; the E-type and A-type cyclins, which activate Cdk2 to effect events in S phase including DNA replication and centrosome duplication; and A-type cyclins (in a second role) and B-type cyclins, which activate Cdk1 to direct structural and regulatory events in mitosis. Inactivation of Cdk1 in late mitosis contributes to reset the cell in G1.

An important role of Cdks is in the phosphorylation of the retinoblastoma (Rb) tumor suppression gene product whereafter E2F is released to facilitate DNA replication and progression through the cell cycle (McLaughlin et al., Drug Discovery Today. 8: 793-802 (2003)).

Cdk deregulation, either through direct or indirect mechanisms, is a typical feature in most cancer cells. Furthermore there exist a plethora of biological mechanistic indications and convincing support by preclinical studies, that Cdk inhibitors can synergise with various chemotherapeutic agents in tumor cell killing (Fisher et al. Expert Opin. Investig. Drugs. 12: 955-970 (2003)).

Also Aurora kinases play critical roles in cell division and chromosome segregation. They are implicated in the centrosome cycle, spindle assembly, chromosome condensation, microtubule-kinetochore attachment, the spindle checkpoint and cytokinesis. Aurora kinases are regulated through phosphorylation, the binding of specific partners and ubiquitin-dependent proteolysis. The deregulation of Aurora kinases impairs spindle assembly, spindle checkpoint function and cell division, causing mis-segregation of individual chromosomes or polyploidization accompanied by centrosome amplification. Aurora kinases are frequently overexpressed in cancers and the identification of Aurora A as a cancer-susceptibility gene provides a strong link between mitotic errors and carcinogenesis.

Thus pharmacological cell cycle specific kinase inhibition is an attractive strategy towards mechanism-based therapies in proliferative disorders. Moreover, the combination of cell cycle specific kinases inhibition with existing chemotherapy can have advantages effects.

Background of the invention

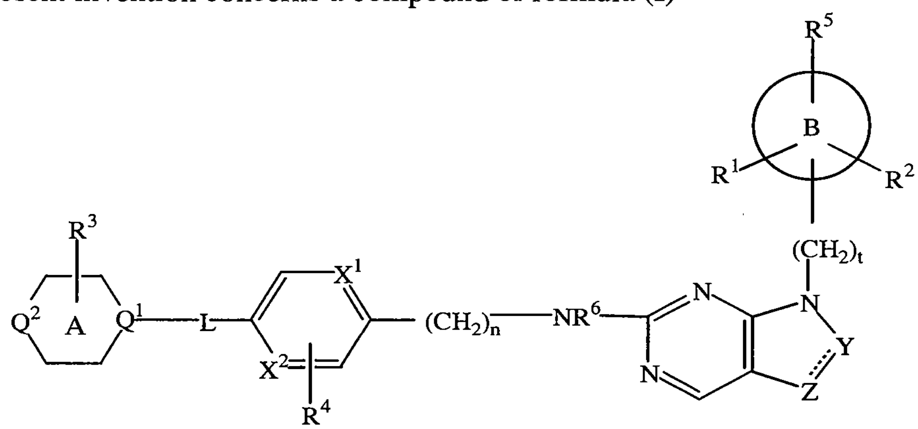
European patent application EP0961775 A2, published on 23 April 1998, discloses purine L-nucleoside compounds and compositions that may be used in inflammation, infections, infestations, neoplasms, and autoimmune disease. More in particular these compounds are described as being modulators of Th1 and Th2.
European patent application EP1147108 A1, published on 27 July 2000, discloses substituted nitrogen heterocyclic derivatives having immunosuppressive, antimicrobial, cytostatic, anticancer, antimitotic and antineurogenerative effects. More in particular these compounds are described as suppressors of spontaneous and mitogen activated lymphocytes and as antiviral compounds. European patent application EP1244668 A1, published on 12 July 2001, discloses purine derivatives with an inhibitory effect on cyclin dependent kinases, viruses and proliferation of haematopoitic and cancer cells. More in particular the compounds are described as inhibitors of the cyclin dependent kinases that associate with type B cyclin, f.e. cdk1 and related cdks (cdk2, cdk5, cdk7 and cdk9).
European patent aplication EP1507780, published on 4 december 2003, discloses pyrazolo-pyrimidine aniline compounds, useful as kinase inhibitors.
European application EP153976 A2, published on 4 March 2004, describes 2,6,9-trisubstituted 8-azapurines as kinase inhibitors.
European patent application EP1590341 A1, published on 5 August 2004, discloses pyrimidine derivatives with an inhibitory activity on cyclin-dependent kinase 4.

European patent application EP1615926 A1, published on 4 november 2004, discloses purin-6-yl amino acid derivatives as anti-cancer agents.
International application WO 03/63764, published on 9 december 2004, discloses 6-substituted pyrazolo[3, 4-d]pyrimidin-4-ones useful as cyclin dependent kinase inhibitors

The present invention relates to compounds, which are distinguishable from the prior art in structure, pharmacological activity, potency and selectivity.

<u>Description of the invention</u>

The present invention concerns a compound of formula (I)



(I),

a *N*-oxide, an addition salt, a quaternary amine and a stereochemically isomeric form thereof, wherein

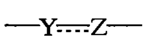
X^1 and X^2 are each independently N or CH with the exception that X^1 and X^2 can not be both N;

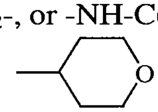
Q^1 is CH_2, or N;

Q^2 is CH_2, N, or O;

n is an integer with value 0 or 1 and when n is 0 then a direct bond is intended;

t is an integer with value 0 or 1 and when t is 0 then a direct bond is intended;

 is –CH=N-, –C(=O)-NH-, –N=CH-, –C(=O)-CH_2-, or -NH-C(=O)-;

ring B represents phenyl, cyclopentyl, cyclohexyl, narbonyl or  ;

L is a direct bond, $-(CH_2)_r-NR^7-(CH_2)_s-$, $-(CR^8{}_2)_r-O-(CH_2)_s-$, $-C(=O)-$, $-(CH_2)_r-O-C(=O)-$, $-(CH_2)_r-NR^7-C(=O)-$, $-S(=O)_2-$, $-(CH_2)_r-NH-S(=O)_2-$, or $-C_{1-6}$alkyl-; wherein
each $-(CH_2)_r-$ moiety is linked to ring A;
each s is an integer with value 0 or 1 and when s is 0 then a direct bond is intended;
each r is an integer with value 0, 1, 2 or 3 and when r is 0 then a direct bond is intended;
each R^7 is hydrogen, C_{1-6}alkyl or C_{1-4}alkyloxycarbonyl;
each R^8 is independently hydrogen, hydroxy or C_{1-6}alkyl; or
two R^8 together can form a bivalent radical of formula $-CH_2-CH_2-$;

R^1, R^2 and R^5 are each independently hydrogen, hydroxy or C_{1-6}alkyl;

R^3 is hydrogen, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxycyclopropylC_{1-6}alkyl, hydroxycyclopropylcarbonyl, hydroxyC_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxyC_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-4}alkyloxycarbonyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxyC_{1-6}alkyl, pyridinyl, $-NR^9R^{10}$, or $-S(=O)_2-NR^9R^{10}$;
wherein each R^9 and R^{10} independently represent hydrogen, C_{1-6}alkyl, C_{1-4}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, hydroxycyclopropylC_{1-6}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl;

R^4 is hydrogen or halo;

R^6 is hydrogen, C_{1-6}alkyl or C_{1-4}alkyloxycarbonyl.

The compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

A number of terms used in the foregoing definitions and hereinafter are explained hereunder. These terms are sometimes used as such or in composite terms.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C_{1-4}alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, e.g. methyl, ethyl, propyl, butyl,

1-methylethyl, 2-methylpropyl and the like; C_{1-6}alkyl includes C_{1-4}alkyl and the higher homologues thereof having 5 to 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like.

The term "addition salt" comprises the salts which the compounds of formula (I) are able to form with organic or inorganic bases such as amines, alkali metal bases and earth alkaline metal bases, or quaternary ammonium bases, or with organic or inorganic acids, such as mineral acids, sulfonic acids, carboxylic acids or phosphorus containing acids.

The term "addition salt" further comprises pharmaceutically acceptable salts, metal complexes and solvates and the salts thereof, that the compounds of formula (I) are able to form.

The term "pharmaceutically acceptable salts" means pharmaceutically acceptable acid or base addition salts. The pharmaceutically acceptable acid or base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and non-toxic base addition salt forms which the compounds of formula (I) are able to form. The compounds of formula (I) which have basic properties can be converted in their pharmaceutically acceptable acid addition salts by treating said base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.
The compounds of formula (I) which have acidic properties may be converted in their pharmaceutically acceptable base addition salts by treating said acid form with a suitable organic or inorganic base. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.
The terms acid or base addition salt also comprise the hydrates and the solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term "metal complexes" means a complex formed between a compound of formula

(I) and one or more organic or inorganic metal salt or salts. Examples of said organic or inorganic salts comprise the halogenides, nitrates, sulfates, phosphates, acetates, trifluoroacetates, trichloroacetates, propionates, tartrates, sulfonates, e.g. methylsulfonates, 4-methylphenylsulfonates, salicylates, benzoates and the like of the metals of the second main group of the periodical system, e.g. the magnesium or calcium salts, of the third or fourth main group, e.g. aluminium, tin, lead as well as the first to the eighth transition groups of the periodical system such as, for example, chromium, manganese, iron, cobalt, nickel, copper, zinc and the like.

The term “stereochemically isomeric forms of compounds of formula (I)”, as used hereinbefore, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of formula (I) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

The *N*-oxide forms of the compounds of formula (I) are meant to comprise those compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide, particularly those *N*-oxides wherein one or more of the piperidine-, piperazine or pyridazinyl-nitrogens are *N*-oxidized.

Whenever used hereinafter, the term "compounds of formula (I)" is meant to include also the N-oxide forms, the pharmaceutically acceptable acid or base addition salts and all stereoisomeric forms.

As used herein before, the term (=O) forms a carbonyl moiety when attached to a carbon atom, a sulfoxide moiety when attached to a sulfur atom and a sulfonyl moiety when two of said terms are attached to a sulfur atom.

Lines drawn into ring systems from substituents indicate that the bond may be attached to any of the suitable ring atoms of the ring system.

A first group of interesting compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply:

a) n is 0;

b) t is 0;

c) L is a direct bond, $-(CH_2)_r-NR^7-(CH_2)_s-$, $-C(=O)-$, $-(CH_2)_r-NR^7-C(=O)-$, $-S(=O)_2-$ or $-C_{1-6}alkyl-$;

d) s is 1;

e) r is 0 or 2;

f) each R^7 is hydrogen or C_{1-4}alkyloxycarbonyl;

g) R^1, R^2 and R^5 are each independently hydrogen;

h) R^3 is hydrogen, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxycyclopropylcarbonyl, hydroxyC_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyl, C_{1-4}alkyloxycarbonyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, pyridinyl, $-NR^9R^{10}$, or $-S(=O)_2-NR^9R^{10}$;

i) each R^9 and R^{10} independently represent hydrogen, C_{1-4}alkyloxycarbonyl or C_{1-6}alkyloxyC_{1-6}alkyl; and

j) R^6 is hydrogen or C_{1-4}alkyloxycarbonyl.

A second group of interesting compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply:

a) X^1 and X^2 are each CH;

b) Q^2 is N, or O;

c) n is 0;

d) t is 0;

e) $-Y{=}Z-$ is $-N{=}CH-$;

f) ring B represents cyclohexyl or narbonyl;

g) L is a direct bond, $-(CH_2)_r-NR^7-(CH_2)_s-$, $-C(=O)-$ or $-C_{1-6}alkyl-$;

h) s is 1;

i) r is 0 or 2;

j) each R^7 is hydrogen;

k) R^1, R^2 and R^5 are each independently hydrogen;

l) R^3 is hydrogen, C_{1-6}alkyl or hydroxyC_{1-6}alkyl;

m) R^4 is hydrogen; and

n) R^6 is hydrogen.

A third group of interesting compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply:

a) X^1 and X^2 are each CH;

b) Q^1 is N;

c) Q^2 is N;

d) n is 0;
e) t is 0;
f) $-Y\overset{\cdots}{-}Z-$ is –N=CH-;
g) L is a direct bond or methyl;
h) R^1, R^2 and R^5 are each independently hydrogen;
k) R^3 isC_{1-6}alkyl;
l) each R^9 and R^{10} independently represent hydrogen, C_{1-4}alkyloxycarbonyl, C_{1-6}alkyloxyC_{1-6}alkyl;
m) R^4 is hydrogen; and
n) R^6 is hydrogen.

A fourth group of interesting compounds consists of those compounds of formula (I) and those compounds of the above mentioned groups wherein $-Y\overset{\cdots}{-}Z-$ is –N=CH-.

A fifth group of interesting compounds consists of those compounds of formula (I) and those compounds of the above mentioned groups wherein ring B represents cyclohexyl or narbonyl.

A sixth group of interesting compounds consists of those compounds of formula (I) and those compounds of the above mentioned groups wherein Q^1 is N and L is a direct bond, -C(=O)-, or methyl.

A seventh group of interesting compounds consists of those compounds of formula (I) and those compounds of the above mentioned groups wherein Q^1 is CH_2 and L is -$(CH_2)_r$–NR^7-CH_2- .

A ninth group of interesting compounds consists of those compounds of formula (I) and those compounds of the above mentioned groups wherein R^3, R^6, R^7, R^9, R^{10}, are other than C_{1-4}alkyloxycarbonyl.

A tenth group of interesting compounds consists of those compounds of formula (I) and those compounds of the above mentioned groups wherein X^1 and X^2 are each CH.

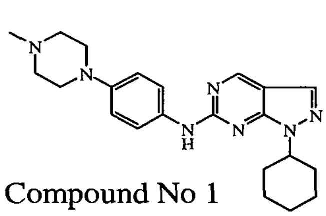
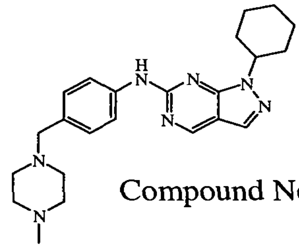
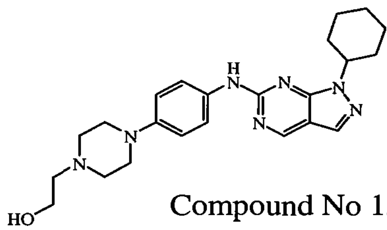
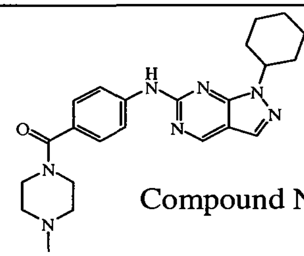
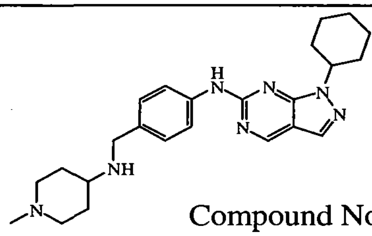
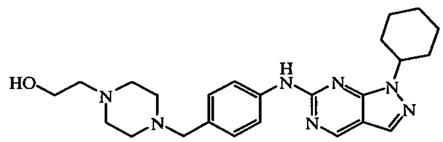
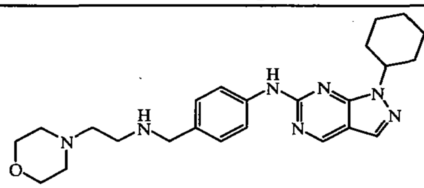
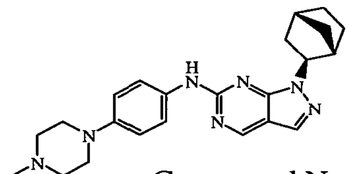
A group of preferred compounds consists of those compounds of formula (I) wherein n is 0; t is 0; L is a direct bond, -$(CH_2)_r$–NR^7-$(CH_2)_s$-, -C(=O)-, -$(CH_2)_r$-NR^7-C(=O)-,

$-S(=O)_2-$ or $-C_{1-6}$alkyl-; s is 1; r is 0 or 2; each R^7 is hydrogen or C_{1-4}alkyloxycarbonyl; R^1, R^2 and R^5 are each independently hydrogen; R^3 is hydrogen, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxycyclopropylcarbonyl, hydroxyC_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyl, C_{1-4}alkyloxycarbonyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, pyridinyl, $-NR^9R^{10}$, or $-S(=O)_2-NR^9R^{10}$; each R^9 and R^{10} independently represent hydrogen, C_{1-4}alkyloxycarbonyl or C_{1-6}alkyloxyC_{1-6}alkyl; and R^6 is hydrogen or C_{1-4}alkyloxycarbonyl.

A group of more preferred compounds consists of those compounds of formula (I) wherein X^1 and X^2 are each CH; Q^2 is N, or O; n is 0; t is 0; $-Y{\cdots}Z-$ is $-N=CH-$; ring B represents cyclohexyl or narbonyl; L is a direct bond, $-(CH_2)_r-NR^7-(CH_2)_s-$, $-C(=O)-$ or $-C_{1-6}$alkyl-; s is 1; r is 0 or 2; each R^7 is hydrogen; R^1, R^2 and R^5 are each independently hydrogen; R^3 is hydrogen, C_{1-6}alkyl or hydroxyC_{1-6}alkyl; R^4 is hydrogen; and R^6 is hydrogen.

Another group of more preferred compounds consists of those compounds of formula (I) wherein X^1 and X^2 are each CH; Q^2 is N, or O; n is 0; t is 0; $-Y{\cdots}Z-$ is $-N=CH-$; ring B represents cyclohexyl or narbonyl; L is a direct bond, $-NH-CH_2-$, $-C(=O)-$ or methyl; R^1, R^2 and R^5 are each independently hydrogen; R^4 is hydrogen; and R^6 is hydrogen.

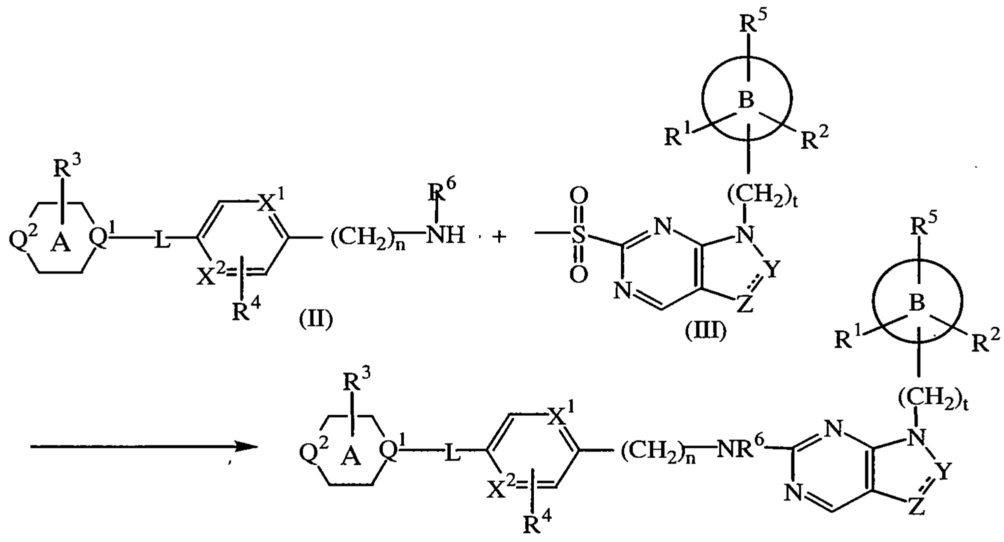
The most preferred compounds are compound No 1, compound No 2, compound No 15, compound No 3, compound No 60, compound No 37, compound No 4 and compound No 23.

 Compound No 1	 Compound No 2
 Compound No 15	 Compound No 3
 Compound No 60	 Compound No 37
 Compound No 4	 Compound No 23

The compounds of formula (I), their pharmaceutically acceptable salts and N-oxides and stereochemically isomeric forms thereof may be prepared in conventional manner. The starting materials and some of the intermediates are known compounds and are commercially available or may be prepared according to conventional reaction procedures as generally known in the art.

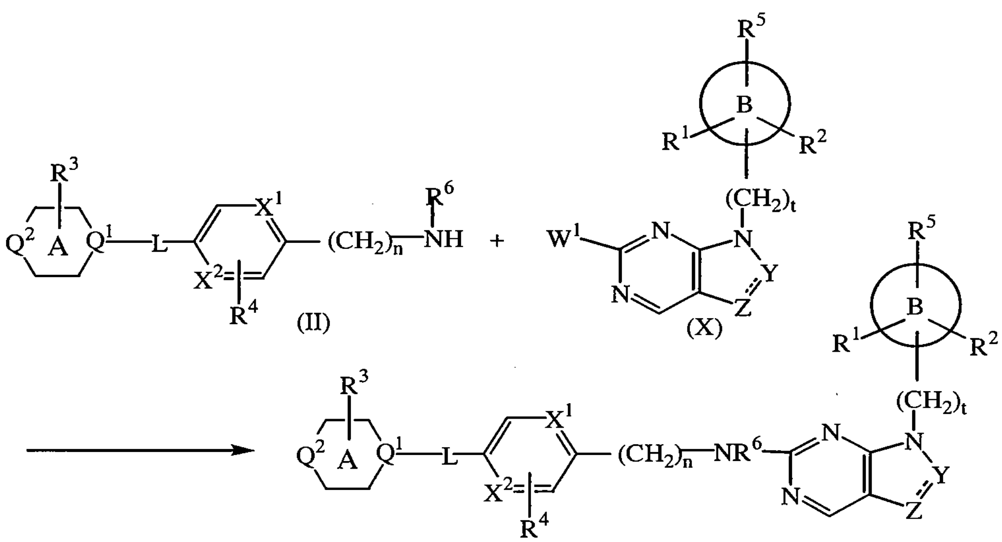
A number of such preparation methods will be described hereinafter in more detail.

Compounds of formula (I) can be prepared by reacting an intermediate of formula (II) with an intermediate of formula (III) in the presence of a suitable solvent, such as for example $(CH_3)_2N\text{-}C(=O)H$, dimethylsulfoxide, $CH_3\text{-}O\text{-}CH_2\text{-}CH_2\text{-}OH$, an alcohol, e.g. 2-propanol and the like, optionally in the presence of a suitable base, such as for example *N,N*-diisopropylethanamine, NaH or 2,6-dimethylpyridine.



(I)

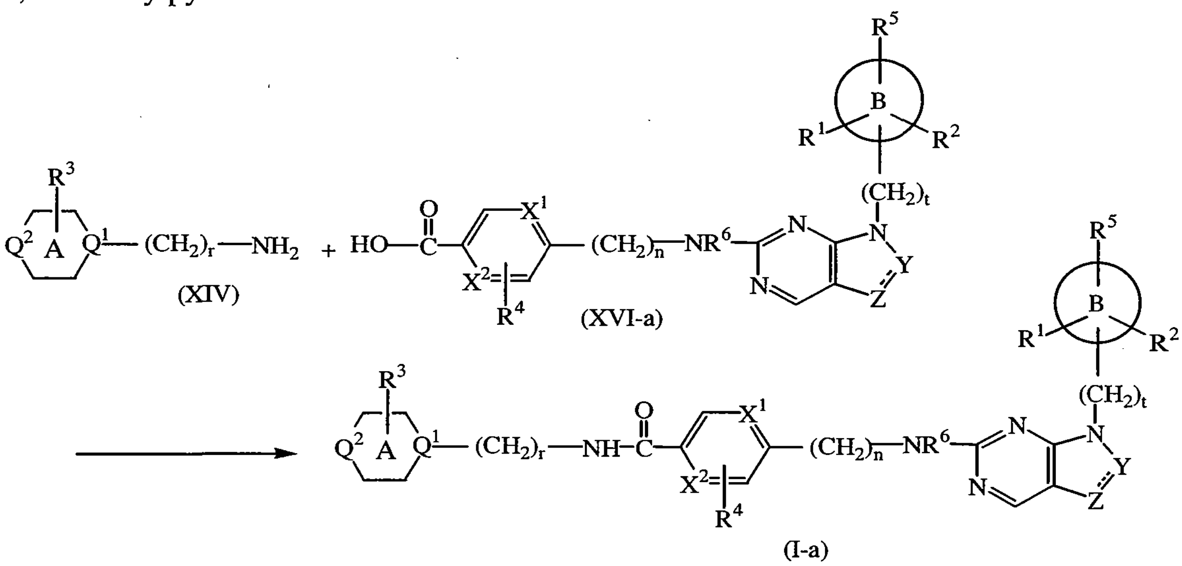
Compounds of formula (I) can also be prepared by reacting an intermediate of formula (X), wherein W^1 is a suitable leaving group such as halogen, for example chloro and the like, with an intermediate of formula (II) in the presence of a suitable solvent, such as for example $(CH_3)_2N\text{-}C(=O)H$, dimethylsulfoxide, $CH_3\text{-}O\text{-}CH_2\text{-}CH_2\text{-}OH$ or an alcohol, e.g. 2-propanol and the like, optionally in the presence of a suitable base, such as for example *N,N*-diisopropylethanamine, NaH or 2,6-dimethylpyridine.



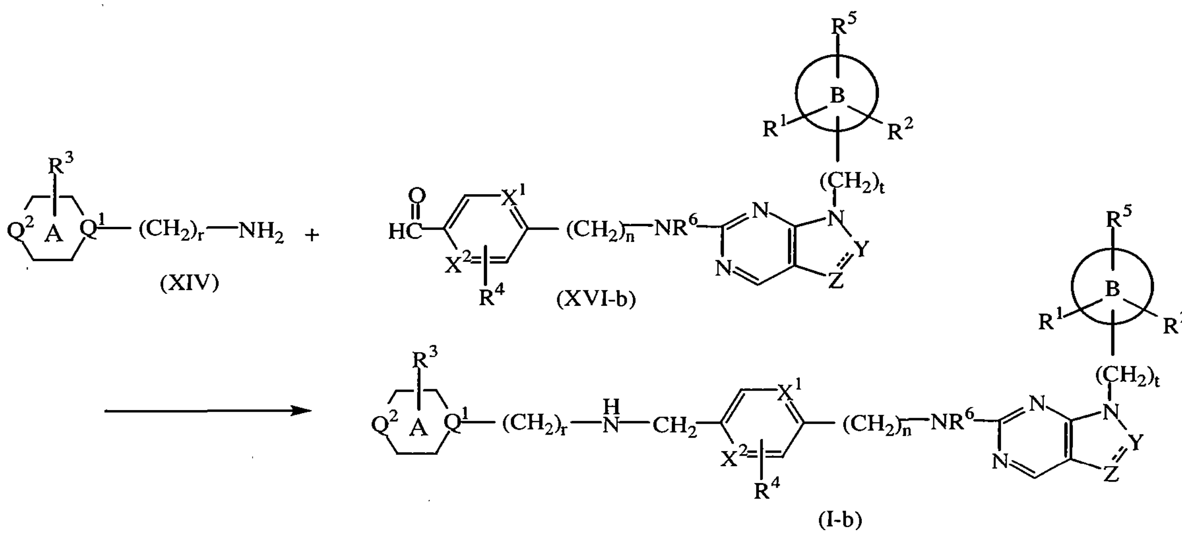
(I)

Compounds of formula (I) wherein L is $-(CH_2)_r\text{–}NH\text{-}C(=O)\text{-}$, herein referred to as compounds of formula (I-a), can also be prepared by reacting an intermediate of formula (XIV) with an intermediate of formula (XVI-a) in the presence of a suitable

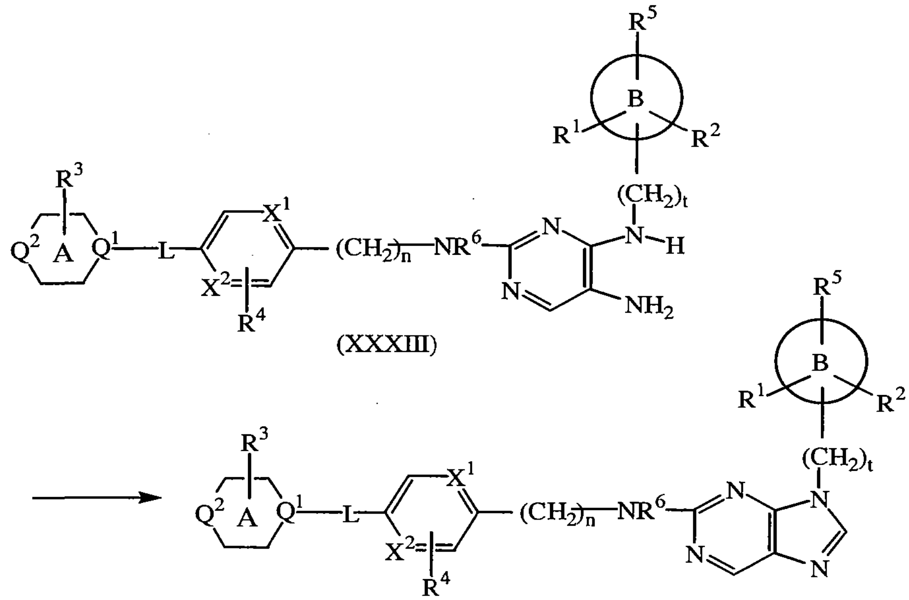
solvent, such as for example $(CH_3)_2N\text{-}C(=O)H$, dimethylsulfoxide, $CH_3\text{-}O\text{-}CH_2\text{-}CH_2\text{-}OH$ or an alcohol, e.g. 2-propanol and the like, optionally in the presence of a suitable base, such as for example *N,N*-diisopropylethanamine, NaH or 2,6-dimethylpyridine.



Compounds of formula (I) wherein L is $-(CH_2)_r\text{-}NH\text{-}(CH_2)\text{-}$, herein referred to as compounds of formula (I-b) can also be prepared by reacting intermediates of formula (XIV) with intermediates of formula (XVI-b) in the presence of sodium triacetoxyborohydride or sodium cyanoborohydride, in the presence of a suitable acid, such as acetic acid and in a suitable solvent, such as for example methanol or tetrahydrofuran.



Compounds of formula (I), wherein —Y⋯Z— is –CH=N-, herein refered to as compounds of formula (I-c) can be prepared by cyclizing an intermediate of formula (XXXIII) in the presence of a salt, such as for example Gold's reagent, or an acid, such as for example formic acid, in a suitable solvent, such as for example dioxane or thriethoxymethane



(I-c)

In the above reactions, the obtained compound of formula (I) can be isolated, and, if necessary, purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography. In case the compound of formula (I) crystallizes out, it can be isolated by filtration. Otherwise, crystallization can be caused by the addition of an appropriate solvent, such as for example water; acetonitrile; an alcohol, such as for example methanol; and combinations of said solvents. Alternatively, the reaction mixture can also be evaporated to dryness, followed by purification of the residue by chromatography (e.g. reverse phase HPLC, flash chromatography and the like). The reaction mixture can also be purified by chromatography without previously evaporating the solvent. The compound of formula (I) can also be isolated by evaporation of the solvent followed by recrystallisation in an appropriate solvent, such as for example water; acetonitrile; an alcohol, such as for example methanol; and combinations of said solvents.
The person skilled in the art will recognise which method should be used, which solvent is the most appropriate to use or it belongs to routine experimentation to find the most suitable isolation method.

In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

The compounds of formula (I) may also be converted into each other via art-known reactions or functional group transformations. A number of such transformations are already described hereinabove. Other examples are hydrolysis of carboxylic esters to the corresponding carboxylic acid or alcohol; hydrolysis of amides to the corresponding carboxylic acids or amines; hydrolysis of nitriles to the corresponding amides; amino groups on imidazole or phenyl may be replaced by a hydrogen by art-known diazotation reactions and subsequent replacement of the diazo-group by hydrogen; alcohols may be converted into esters and ethers; primary amines may be converted into secondary or tertiary amines; double bonds may be hydrogenated to the corresponding single bond; an iodo radical on a phenyl group may be converted in to an ester group by carbon monoxide insertion in the presence of a suitable palladium catalyst.

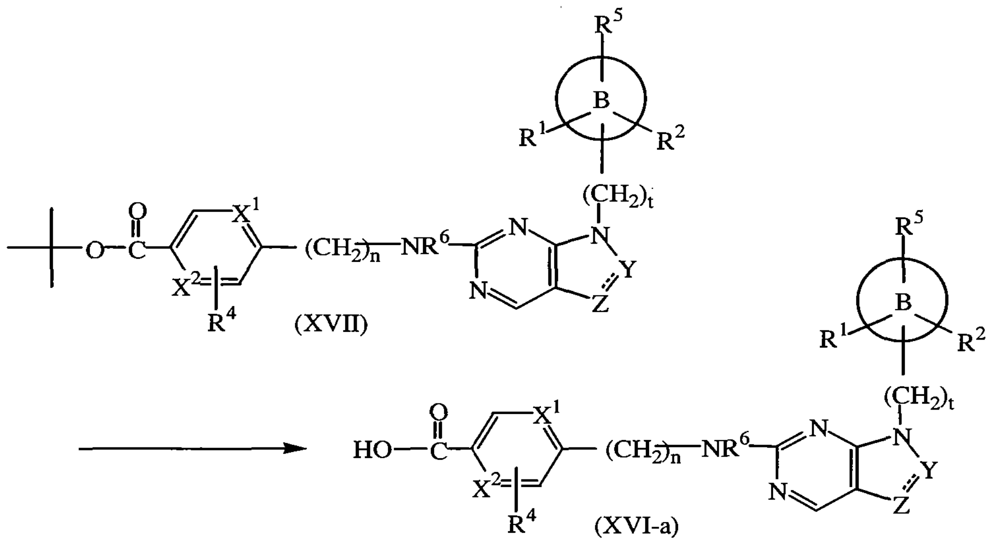
The compounds of formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Some of the compounds of formula (I) and some of the intermediates in the present invention may consist of a mixture of stereochemically isomeric forms. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first

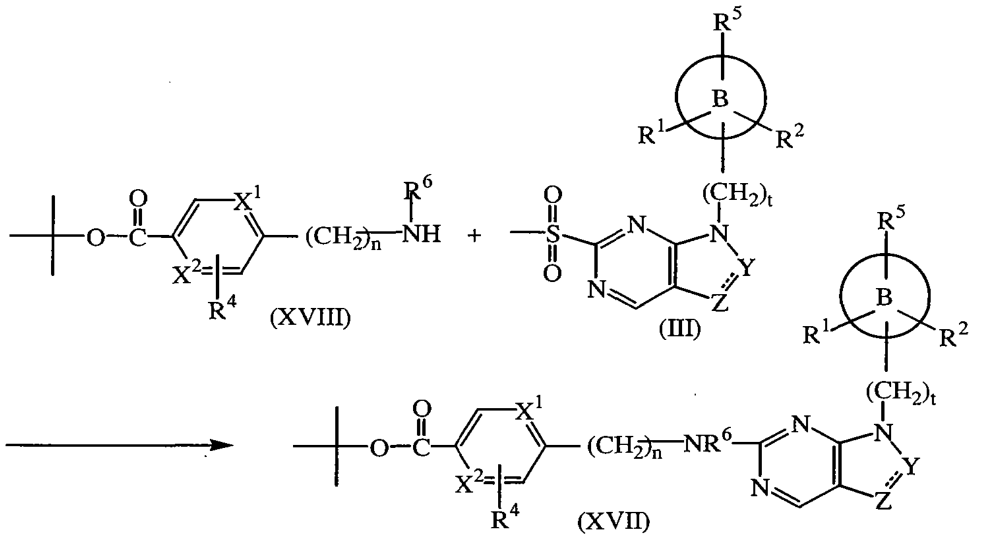
converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

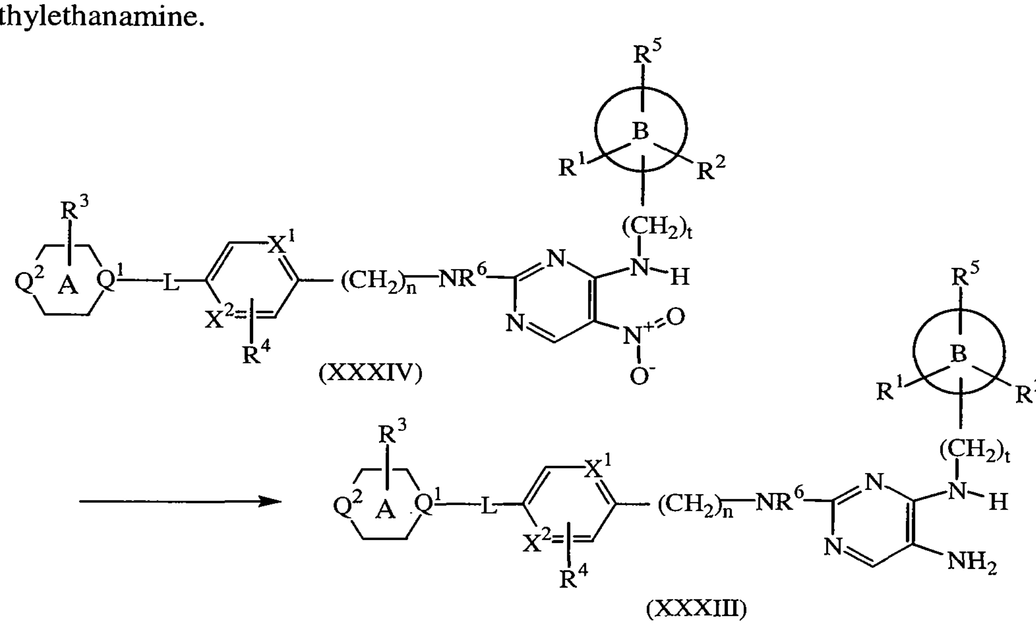
Intermediates of formula (XVI-a) can be prepared by converting of an intermediate of formula (XVII) in the presence of a suitable acid such as trifluoroacetic acid in a suitable solvent such as CH_2Cl_2



Intermediates of formula (XVII) can be prepared by reacting an intermediate of formula (XVIII) with an intermediate of formula (III) in the presence of a suitable solvent, such as for example $(CH_3)_2N\text{-}C(=O)H$, dimethylsulfoxide, $CH_3\text{-}O\text{-}CH_2\text{-}CH_2\text{-}OH$ or an alcohol, e.g. 2-propanol and the like, optionally in the presence of a suitable base, such as for example *N,N*-diisopropylethanamine, Cesium carbonate, NaH or 2,6-dimethylpyridine.

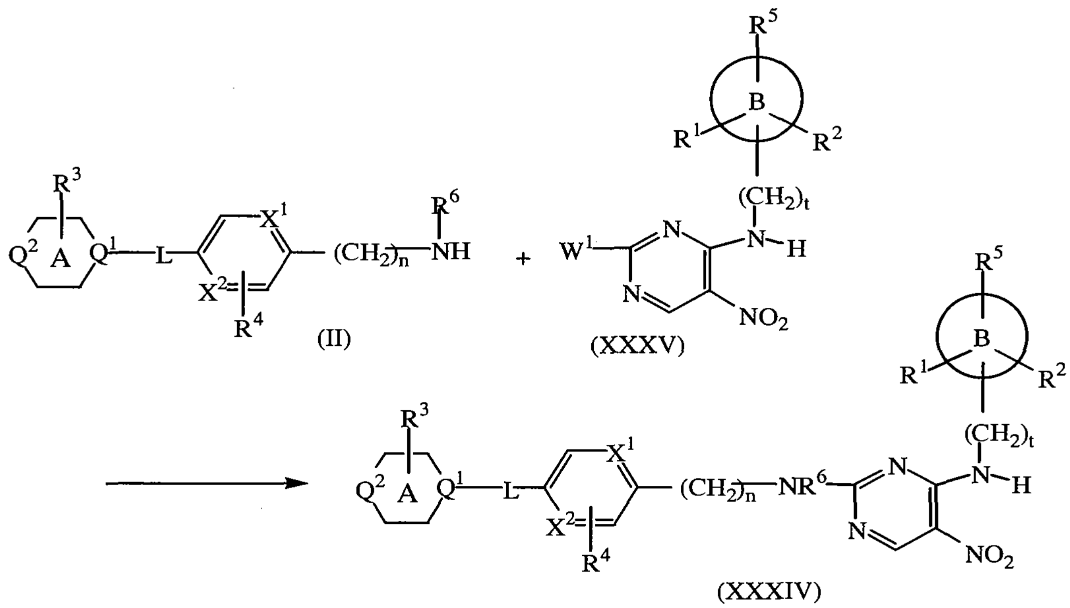


Intermediates of formula (XXXIII) can be prepared by reducing an intermediate of formula (XXXIV) with a suitable reducing agent, such as for example H_2, in the presence of a suitable catalyst, such as for example platina on charcoal or palladium on charcoal, optionally in the presence of a suitable catalyst poison, such as for example a thiophene solution, optionally in the presence of NH_2-NH_2, in the presence of a suitable solvent, such as for example *N*,*N*-dimethylacetamide, tetrahydrofuran, *N*,*N*-dimethylformamide or a suitable alcohol, such as for example methanol, ethanol and the like, and optionally in the presence of a suitable base, such as for example *N*,*N*-diethylethanamine.

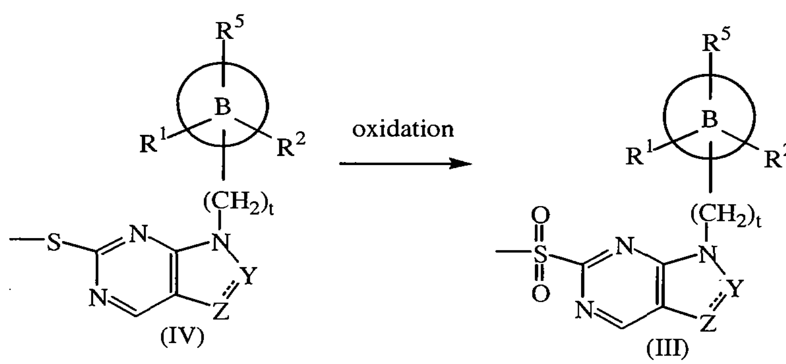


Intermediates of formula (XXXIV) can also be prepared by reacting an intermediate of formula (XXXV) wherein W^1 represents a suitable leaving group such as halogen, for

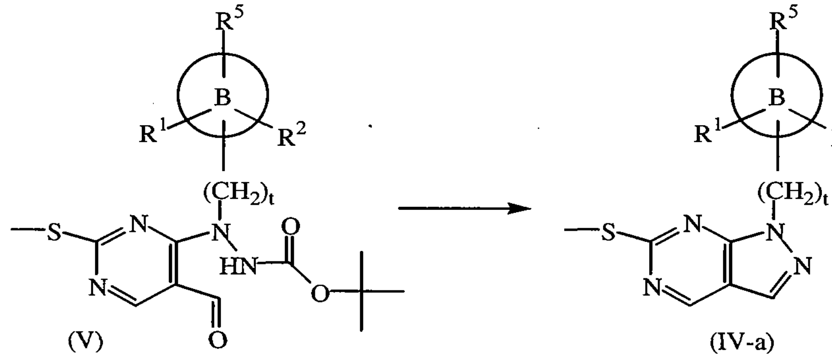
example chloro and the like, with an intermediate of formula (II) in the presence of a suitable base, such as for example *N,N*-diisopropylethanamine or *N,N*-diethylethanamine, and optionally in the presence of a suitable solvent, such as for example *N,N*-dimethylacetamide, *N,N*-dimethylformamide or 1,4-dioxane.



Intermediates of formula (III) can be prepared by reacting an intermediate of formula (IV) with a suitable oxidizing agent, such as for example $KMnO_4$ in the presence of a suitable solvent, such as for example water, and a suitable acid, such as for example acetic acid. An alternative suitable oxidizing agent is meta-chloroperbenzoic acid optionally in the presence of $MgSO_4$, in a suitable solvent, such as for example CH_2Cl_2 and optionally an alcohol, e.g. methanol and the like, optionally in the presence of morpholinomethyl PS and PS-ammonium bicarbonate scavenger.

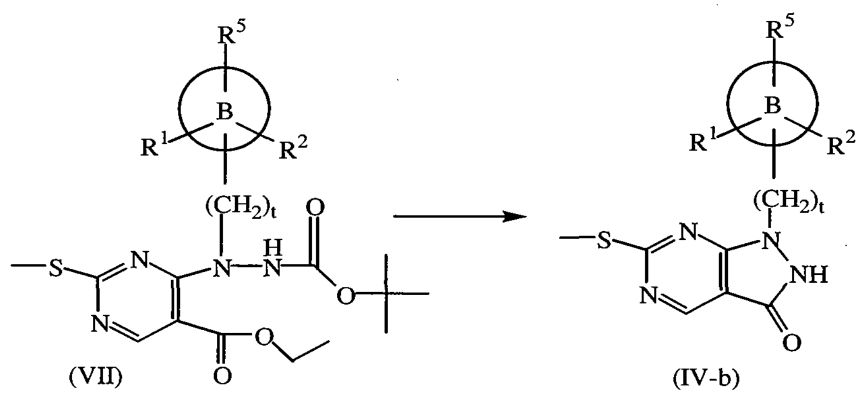


Intermediates of formula (IV), wherein $-Y{\cdots}Z-$ is –N=CH-, herein referred to as intermediates of formula (IV-a) can be prepared by cyclizing an intermediate of formula (V) with a suitable acid, such as for example HCl and the like, in the presence of a suitable solvent, such as for example 2-propanol.



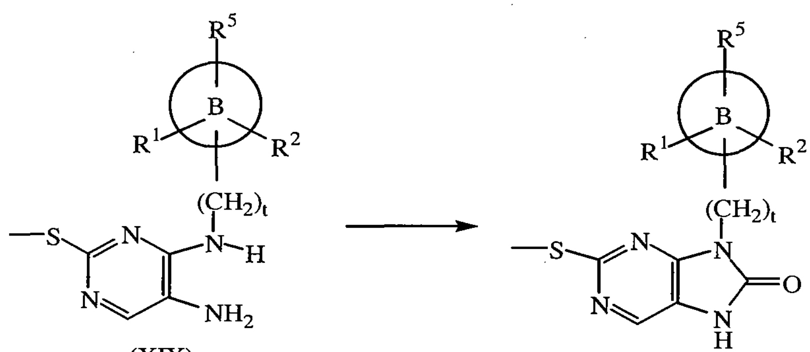
(V) (IV-a)

Intermediates of formula (IV), wherein $-Y{\cdots}Z-$ is –NH-C(=O)-, herein referred to as intermediates of formula (IV-b) can be prepared by cyclizing an intermediate of formula (VII) with a suitable acid, such as for example HCl and the like, in the presence of a suitable solvent, such as for example 2-propanol.



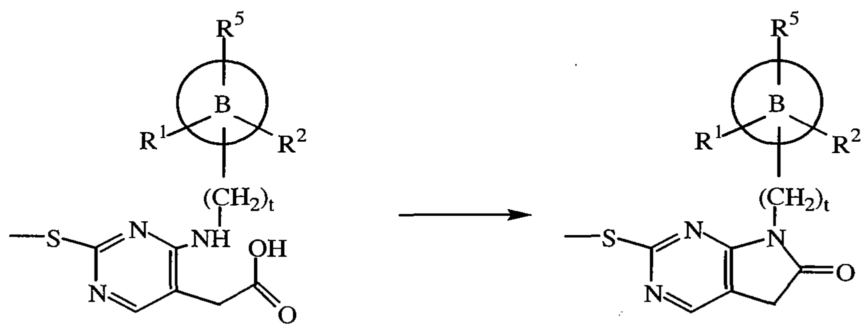
(VII) (IV-b)

Intermediates of formula (IV), wherein $-Y{\cdots}Z-$ is –C(=O)-CH$_2$-, herein referred to as intermediates of formula (IV-c) can be prepared by cyclizing an intermediate of formula (XIX) in the presence of N,N'-methanetetraylbis- 2-propanamine and a suitable solvent, such as for example CH_2Cl_2.



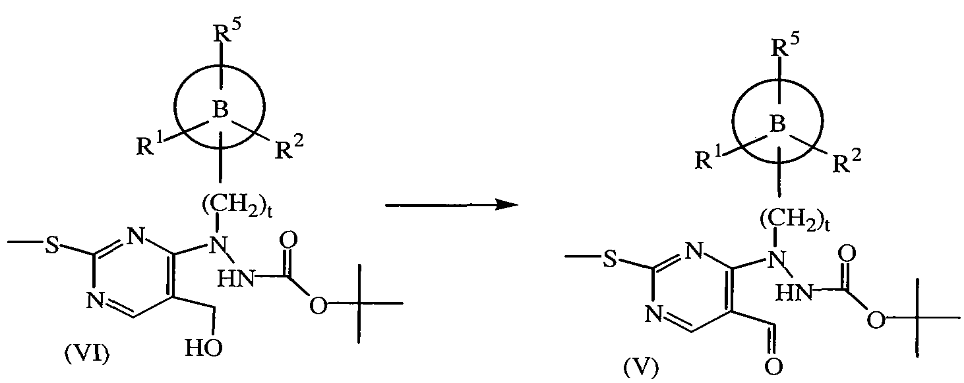
(XIX) (IV-c)

Intermediates of formula (IV), wherein $-Y\text{- - -}Z-$ is –C(=O)-CH_2-, herein referred to as intermediates of formula (IV-d) can be prepared by cyclizing an intermediate of formula (XXV) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and a suitable solvent, such as for example CH_2Cl_2, in the presence of a suitable base, such as for example *N,N*-diisopropylethanamine.



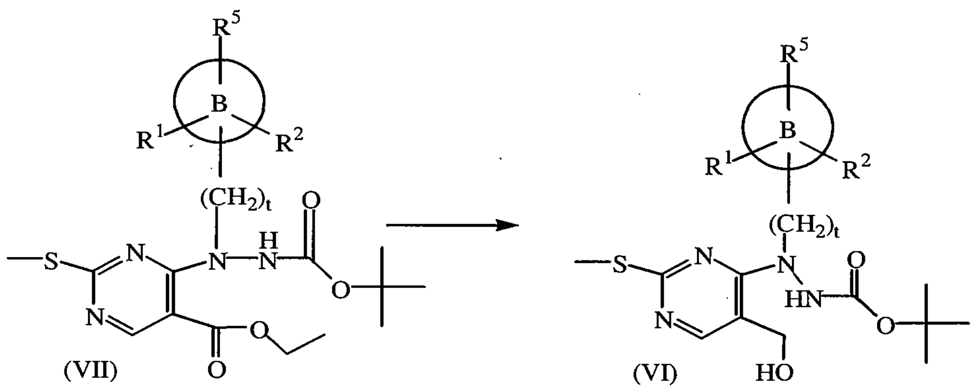
(XXV) (IV-d)

Intermediates of formula (V) can be prepared by reacting an intermediate of formula (VI) with a suitable agent, such as for example MnO_2 in the presence of a suitable solvent, such as for example CH_2Cl_2.

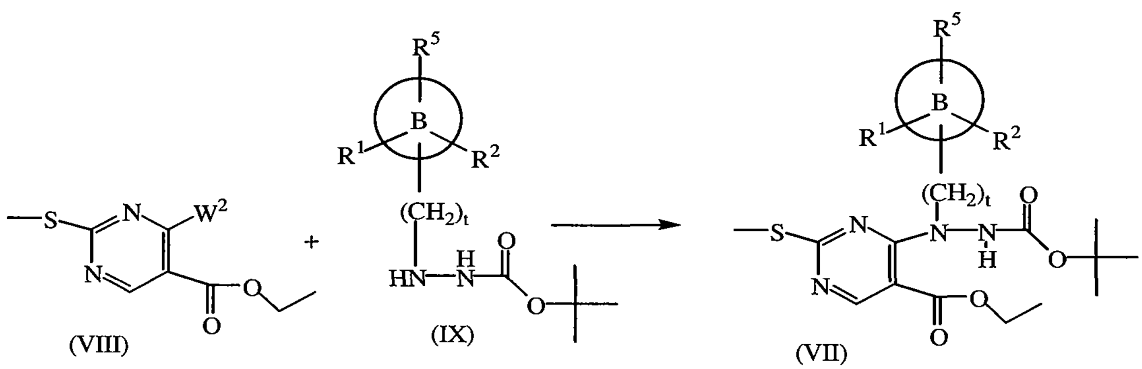


(VI) (V)

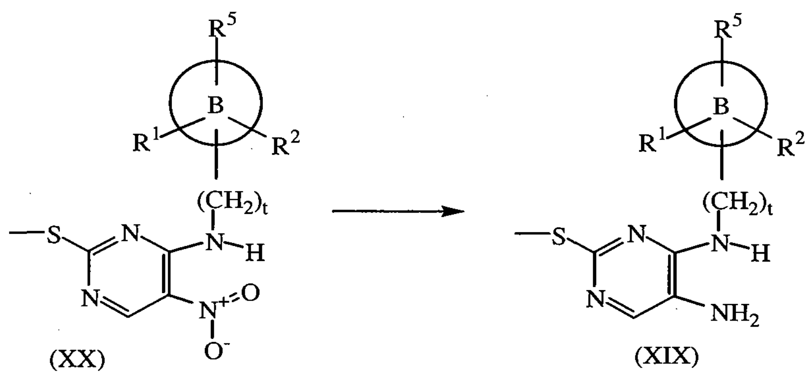
Intermediates of formula (VI) can be prepared by reacting an intermediate of formula (VII) with a suitable agent, such as for example $LiAlH_4$ in the presence of a suitable solvent, such as for example tetrahydrofuran.



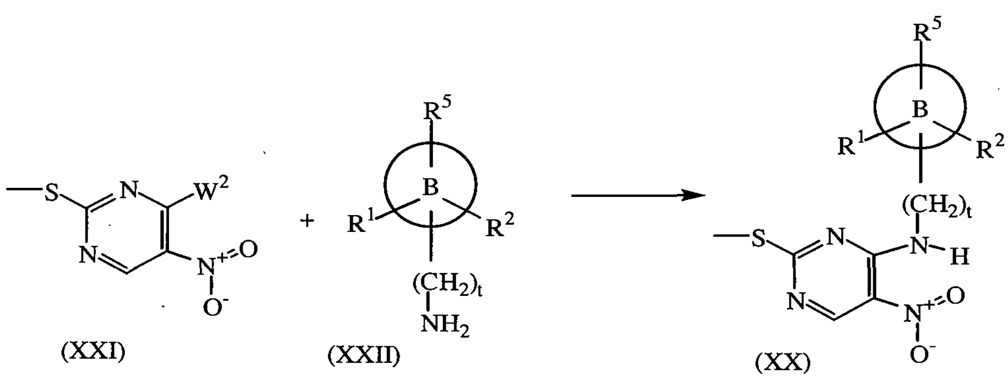
Intermediates of formula (VII) can be prepared by reacting an intermediate of formula (VIII), wherein W^2 represents a suitable leaving group such as halogen, for example. chloro and the like, with an intermediate of formula (IX) in the presence of a suitable solvent, such as for example tetrahydrofuran, in the presence of a suitable base, such as for example *N,N*-diethylethanamine.



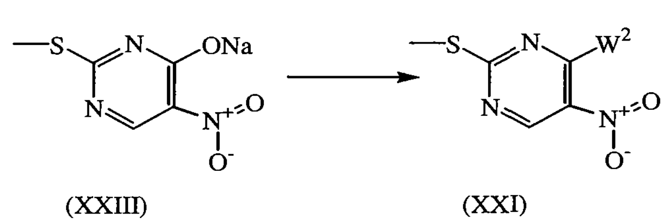
Intermediates of formula (XIX) can be prepared by reducing an intermediate of formula (XX) with a suitable reducing agent, such as for example H_2, in the presence of a suitable catalyst, such as for example platina on charcoal or palladium on charcoal, optionally in the presence of a suitable catalyst poison, such as for example a thiophene solution, optionally in the presence of NH_2-NH_2, in the presence of a suitable solvent, such as for example *N,N*-dimethylacetamide, tetrahydrofuran, *N,N*-dimethylformamide or a suitable alcohol, such as for example methanol, ethanol and the like, and optionally in the presence of a suitable base, such as for example *N,N*-diethylethanamine.



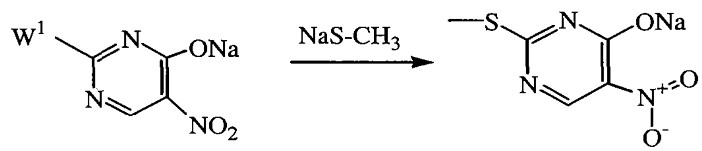
Intermediates of formula (XX) can be prepared by reacting an intermediate of formula (XXI), wherein W^2 represents a suitable leaving group such as halogen, for example. chloro and the like, with an intermediate of formula (XXII) in the presence of a suitable base, such as for example *N,N*-diisopropylethanamine or *N,N*-diethylethanamine, and optionally in the presence of a suitable solvent, such as for example *N,N*-dimethylacetamide, *N,N*-dimethylformamide, acetonitrile or 1,4-dioxane.



Intermediates of formula (XXI) can be prepared by reacting an intermediate of formula (XXIII) with $POCl_3$.

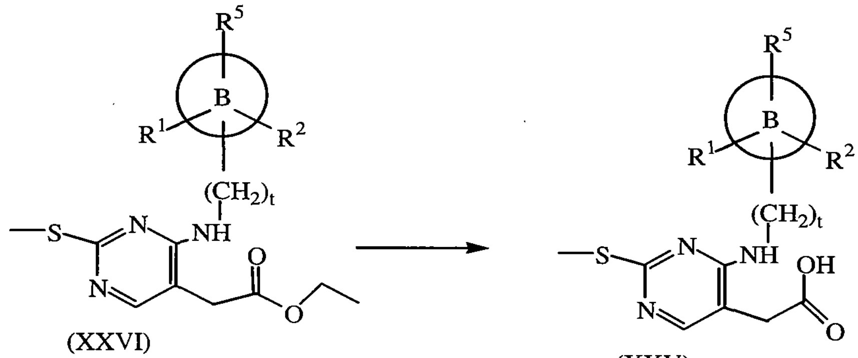


Intermediates of formula (XXIII) can be prepared by reacting an intermediate of formula (XXIV), wherein W^1 represents a suitable leaving group such as halogen, for example. chloro and the like, in the presence of $NaS\text{-}CH_3$ in water, in a suitable solvent, such as for example ethanol.



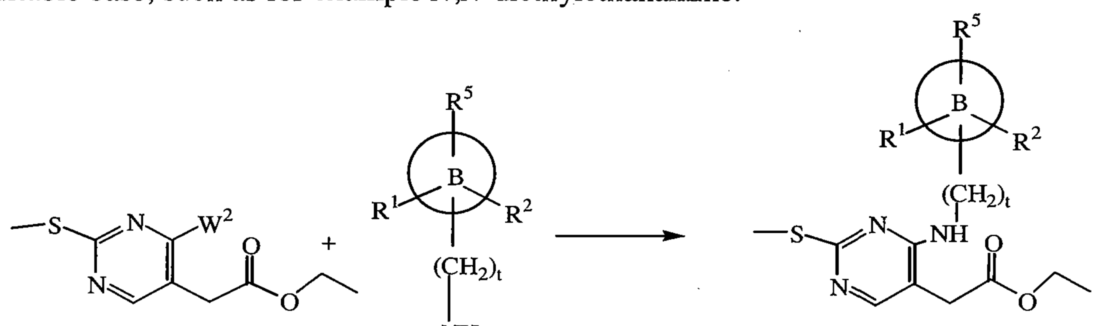
(XXIV) (XXIII)

Intermediates of formula (XXV) can be prepared by reacting an intermediate of formula (XXVI) with a suitable acid, such as for example HCl in the presence of a suitable solvent, such as for example dioxane.



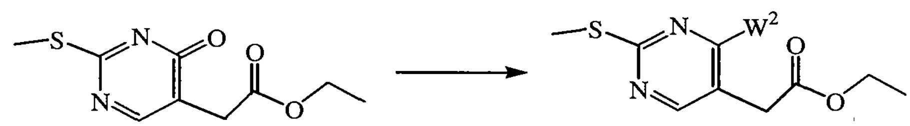
(XXVI) (XXV)

Intermediates of formula (XXVI) can be prepared by reacting an intermediate of formula (XXVII) wherein W^2 represents a suitable leaving group such as halogen, for example chloro and the like, with an intermediate of formula (XXVIII) in the presence of a suitable solvent, such as for example cyclohexylamine, in the presence of a suitable base, such as for example *N*,*N*-diethylethanamine.



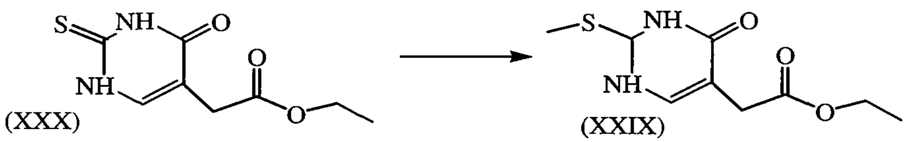
(XXVII) (XXVIII) (XXVI)

Intermediates of formula (XXVII), wherein halo represents for example chloro and the like, can be prepared by reacting an intermediate of formula (XXIX) with $POCl_3$.



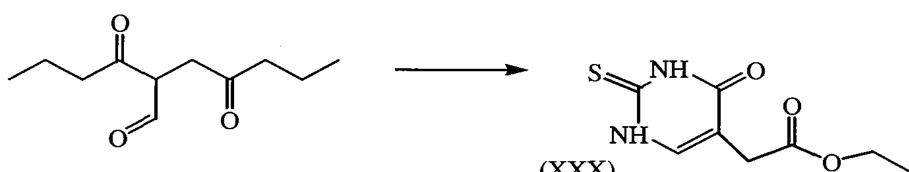
(XXIX) (XXVII)

Intermediates of formula (XXIX) can be prepared by reacting an intermediate of formula (XXX) with iodomethane in the presence of a suitable solvent such as for example a mixture of 2,3,4,6,7,8,9,10-octahydro-pyrimido[1,2-a]azepine and *N,N*-dimethylformamide.



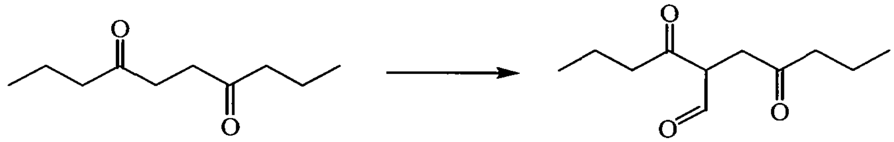
(XXX) (XXIX)

Intermediates of formula (XXX) can be prepared by reacting an intermediate of formula (XXXI) with thiourea in the presence of sodium ethoxylate in a suitable solvent such as ethanol.



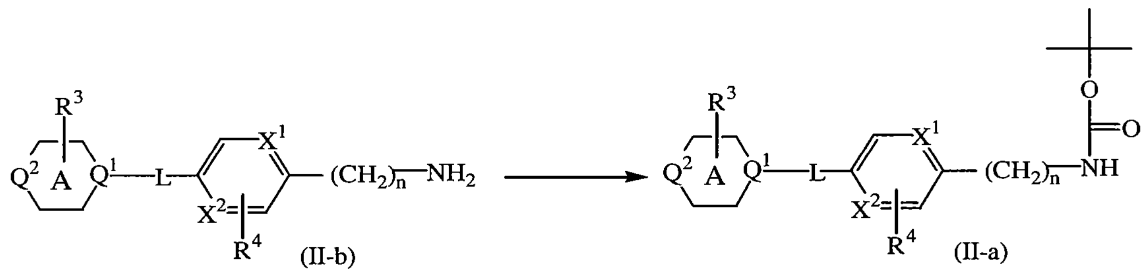
(XXXI) (XXX)

Intermediates of formula (XXXI) can be prepared by reacting an intermediate of formula (XXXII) with H(C=O)-O-CH_2-CH_3 in the presence of NaH in a suitable solvent such as a mixture of ethanol and tetrahydrofuran.

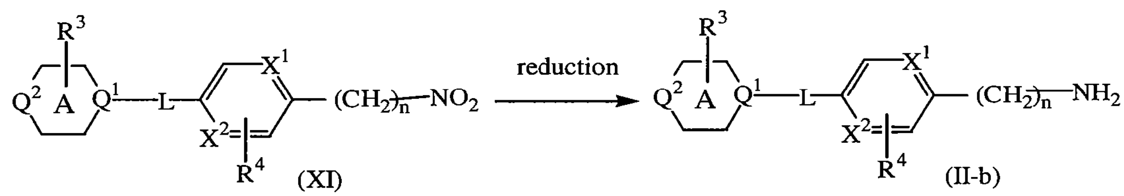


(XXXII) (XXXI)

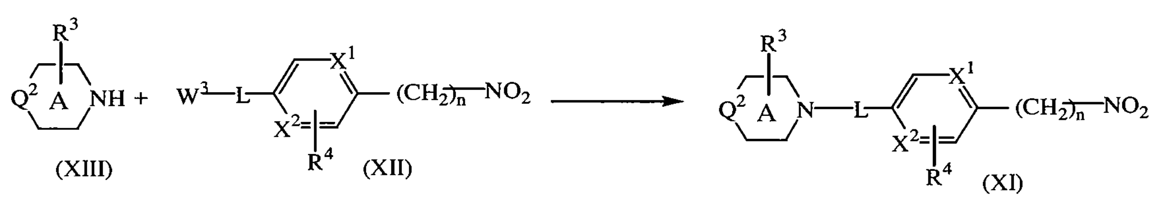
Intermediates of formula (II) wherein R^6 is C_{1-4}alkyloxycarbonyl, such as tertiary butoxycarbonyl, herein referred to as intermediates of formula (II-a), can be prepared by reacting intermediates of formula (II-b) with di-tert-butyl-dicarbonate in the presence of a suitable solvent, such as for example tetrahydrofuran, and optionally in the presence of a suitable base, such as for example *N,N*-diethylethanamine.



Intermediates of formula (II) wherein R^6 represents hydrogen, said intermediates being represented by formula (II-b), can be prepared by reacting an intermediate of formula (XI) with a suitable reducing agent, such as for example H_2, in the presence of a suitable catalyst, such as for example platina on charcoal or palladium on charcoal, optionally a suitable catalyst poison, such as for example a thiophene solution, a suitable solvent, such as for example *N,N*-dimethylacetamide, tetrahydrofuran, *N,N*-dimethylformamide or a suitable alcohol, such as for example methanol, and optionally in the presence of a suitable base, such as for example *N,N*-diethylethanamine.

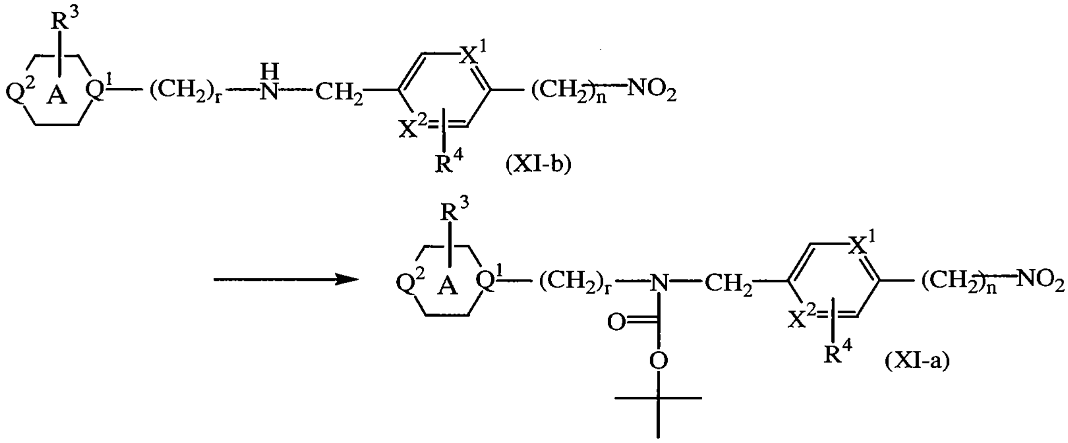


Intermediates of formula (XI) can be prepared by reacting an intermediate of formula (XII), wherein W^3 represents a suitable leaving group such as halogen, for example. chloro and the like, with an intermediate of formula (XIII) in the presence of a suitable solvent, such as for example *N,N*-dimethylacetamide, *N,N*-dimethylformamide, CH_2Cl_2, 1,4-dioxane, or a mixture of CH_2Cl_2 and pyridine and optionally in the presence of a suitable base, such as for example *N,N*-diisopropylethanamine.



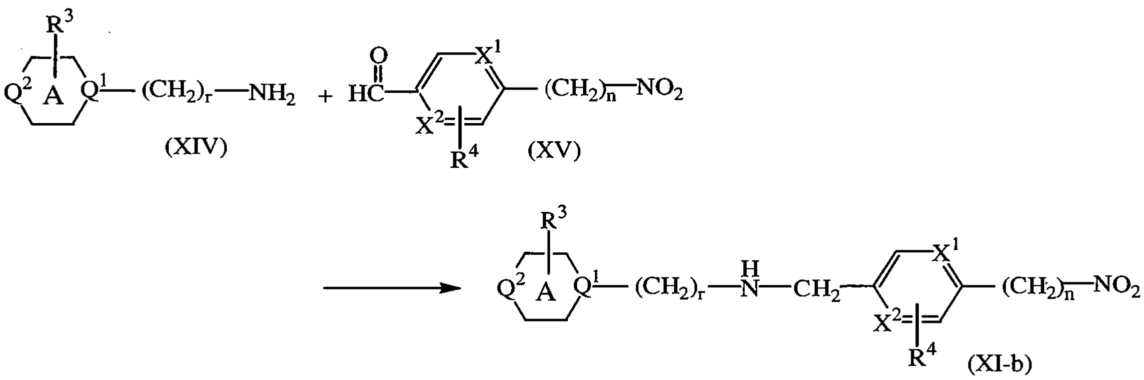
Intermediates of formula (XI) wherein L is $-(CH_2)_r-NR^7-(CH_2)-$ and R^7 is C_{1-4}alkyloxycarbonyl, such as f.e. tertiary butoxycarbonyl, herein referred to as intermediates of formula (XI-a), can be prepared by reacting an intermediate of formula

(XI) wherein L is -$(CH_2)_r$–NR^7-(CH_2)- and R^7 is hydrogen, herein referred to as intermediates of formula (XI-b), with di-tert-butyl-dicarbonate in the presence of a suitable solvent, such as for example tetrahydrofuran, and optionally in the presence of a suitable base, such as for example *N,N*-diethylethanamine.



(XI-b) (XI-a)

Intermediates of formula (XI-b) can be prepared by reacting intermediates of formula (XIV) with intermediates of formula (XV) in the presence of sodium triacetoxyborohydride or sodium cyanoborohydride, in the presence of a suitable acid, such as acetic acid and in a suitable solvent, such as for example methanol or tetrahydrofuran.



(XIV) (XV) (XI-b)

The compounds of formula (I), the pharmaceutically acceptable acid addition salts and stereoisomeric forms thereof have valuable pharmacological properties in that they are selective cell cycle specific kinase inhibitors. Specific inhibitory compounds are superior therapeutic agents since they are characterized by a greater efficacy and lower toxicity by virtue of their specificity.

The term "cell cycle specific kinase inhibitor(s)" or "inhibitor(s) of cell-cycle specific kinases" is used herein to describe an agent that inhibits at least the activity of CDK4, AURORA A and/or AURORA B in the assays described in C (pharmacological examples).

The term "CDK4" is used herein to mean a protein obtained as a result of expression of a cdk4 gene. Within the meaning of this term, CDK4 encompass all proteins encoded by a cdk4 gene, mutants thereof, and alternative slice proteins thereof. Additionally, as used herein, the term "CDK4" includes CDK4 analogues, homologues and analogues of other animals.

The term "AURORA A and/or AURORA B" is used herein to mean a protein obtained as a result of expression of an aurora gene. Within the meaning of this term, AURORA A and/or AURORA B encompass all proteins encoded by an aurora gene, mutants thereof, and alternative slice proteins thereof. Additionally, as used herein, the term "AURORA A and/or AURORA B" includes AURORA A and/or AURORA B analogues, homologues and analogues of other animals.

The term "cell cycle specific kinase", includes, but is not limited to, cyclin dependent kinases and/or aurora kinases.

The term "cyclin dependent kinases", includes but is not limited to CDK4. Within the meaning of this term CDK1, CDK2, CDK3, CDK5, CDK6, CDK7, CDK8 and CDK9 may be encompassed.

Hence, the present invention discloses the compounds of formula (I) for use as a medicine.

Furthermore, the invention also concerns the use of a compound for the manufacture of a medicament for the treatment of a disorder mediated through cell cycle specific kinases.

In particular, the invention concerns the use of a compound for the manufacture of a medicament for the treatment of a disorder mediated through CDK4, AURORA A and/or AURORA B.

Even more in particular, the invention concerns the use of a compound for the manufacture of a medicament for the treatment of a proliferative disorder or a differentiative disorder.

The term "proliferative disorder" is used herein in a broad sense to include any disorder that requires control of the cell cycle, for example cancer; cardiovascular disorders such as f.e. restenosis and cardiomyopathy; auto-immune disorders such as f.e. glomerulonephritis, rheumatoid arthritis, lupus, type I diabetis, and multiple sclerosis; dermatological disorders such as f.e. psoriasis, anti-inflammatory disorders and anti-viral disorders. In these disorders, the compounds of formula (I) may induce apoptosis or maintain stasis within the desired cells as required.

The compounds of the invention may inhibit any of the steps or stages in the cell cycle, such as for example:

- formation of the nuclear envelope,
- exit from the quiescent phase of the cell cycle (G0),
- G1 entry,
- G1 progression,
- chromosome decondensation,
- nuclear envelope breakdown,
- START,
- initiation of DNA replication,
- progression of DNA replication,
- termination of DNA replication,
- centrosome duplication,
- G2 entry,
- G2 progression,
- activation of mitotic or meiotic function,
- chromosome condensation,
- centrosome separation,
- microtubule nucleation,
- spindle formation and/or function,
- interaction with microtubule motor proteins,
- chromatid separation and segregation,
- inactivation of mitotic function,
- formation of the contractile ring, and/or
- cytokinesis functions.

The compounds of the invention may in particular inhibit replication of RNA and DNA viruses that are dependent upon events associated with host cell proliferation and differentiation.

With the term “differentiative disorder” is meant any disorder that results from the de-differentiation of tissue which may (optionally) be accompanied by re-entry in mitosis. Such degenerative disorders include neurodegenerative diseases of the nervous system, such as f.e., Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, or amyotrophic lateral sclerosis as well as spinocerebellar degenerations. Other differentiative disorders include, for example, disorders associated with connective tissue such as may occur due to de-differentiation of chondrocytes or osteocytes, cardiovascular disorders which involve the de-differentiation of endothelial tissue and smooth muscle cells, gastric ulcers characterised by degenerative changes in glandular cells, and renal conditions marked by failure to differentiate.

The term “treating” or "treatment" as used herein covers any treatment of a disease and/or condition in an animal, particularly a human, and includes: (i) preventing a disease and/or condition from occurring in a subject which may be predisposed to the disease and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease and/or condition, i.e., arresting its development; (iii) relieving the disease and/or condition, i.e., causing regression of the disease and/or condition.

This invention also provides a method for treating a disorder mediated through a cell cycle specific kinase by administering an effective amount of a compound of the present invention, to a subject, e.g. a mammal (and more particularly a human) in need of such treatment.

In particular, this invention provides a method for treating a disorder mediated through CDK4, AURORA A and/or AURORA B, by administering an effective amount of a compound of the present invention, to a subject, e.g. a mammal (and more particularly a human) in need of such treatment.

Even more in particular, this invention provides a method for treating a proliferative and/or a differentiative disorder, by administering an effective amount of a compound of the present invention, to a subject, e.g. a mammal (and more particularly a human) in need of such treatment.

Thus, this invention also provides a method for inhibiting tumour growth by administering an effective amount of a compound of the present invention, to a subject, e.g. a mammal (and more particularly a human) in need of such treatment.

Examples of tumours which may be inhibited, but are not limited to, lung cancer (e.g. adenocarcinoma and including non-small cell lung cancer), pancreatic cancers (e.g. pancreatic carcinoma such as, for example exocrine pancreatic carcinoma), colon cancers (e.g. colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), oesophageal cancer, oral squamous carcinoma, tongue carcinoma, gastric carcinoma, nasopharyngeal cancer, hematopoietic tumours of lymphoid lineage (e.g. acute lymphocytic leukemia, B-cell lymphoma, Burkitt's lymphoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), tumours of mesenchymal origin (e.g. fibrosarcomas and rhabdomyosarcomas), melanomas, teratocarcinomas, neuroblastomas, brain tumors, gliomas, benign tumour of the skin (e.g. keratoacanthomas), breast carcinoma (e.g. advanced breast cancer), kidney carcinoma, ovary carcinoma, cervical carcinoma, endometrial carcinoma, bladder carcinoma, prostate cancer including the advanced disease, testicular cancers, osteosarcoma, head and neck cancer and epidermal carcinoma.

In view of their useful pharmacological properties, the subject compounds may be formulated into various pharmaceutical forms for administration purposes.

To prepare the pharmaceutical compositions of this invention, an effective amount of a particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets.

Because of their ease in administration, tablets and capsules represent the most

advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, to aid solubility for example, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient, calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The compound of the invention is administered in an amount sufficient to inhibit cell cycle specific kinases.

In particular, the compound of the invention is administered in an amount sufficient to inhibit CDK4, AURORA A and/or AURORA B or in an amount sufficient to modulate

the interaction between CDK4, AURORA A and/or AURORA B and other genes and/or gene products involved in the cell cycle.

Even more in particular, the compound of the invention is administered in an amount sufficient to inhibit a proliferative disorder and/or a differentiative disorder.

With the term “other genes and/or gene products involved in the cell cycle” is meant for example genes and gene products involved in chromatin binding, formation of replication complexes, replication licensing, phosphorylation or other secondary modification activity, proteolytic degradation, microtubule binding, actin binding, septin binding, microtubule organising centre nucleation activity and binding to components of the cell cycle (signalling) pathway.

Those skilled in the art could easily determine the effective amount from the test results presented hereinafter. In general it is contemplated that a therapeutically effective amount would be from 0.005 mg/kg to 100 mg/kg body weight, and in particular from 0.005 mg/kg to 10 mg/kg body weight. It may be appropriate to administer the required dose as single, two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 0.5 to 500 mg, and in particular 10 mg to 500 mg of active ingredient per unit dosage form.

As another aspect of the present invention, a combination of a cell cycle specific kinase inhibitor of formula (I) with another medicinal agent is envisaged, especially for use as a medicine, more specifically in the treatment of cancer or related diseases.

For the treatment of the above conditions, the compounds of the invention may be advantageously employed in combination with one or more other medicinal agents, more particularly, with other anti-cancer agents. Examples of anti-cancer agents are:

- platinum coordination compounds for example cisplatin, carboplatin or oxalyplatin;
- taxane compounds for example paclitaxel or docetaxel;
- topoisomerase I inhibitors such as camptothecin compounds for example irinotecan or topotecan;
- topoisomerase II inhibitors such as anti-tumour podophyllotoxin derivatives for example etoposide or teniposide;
- anti-tumour vinca alkaloids for example vinblastine, vincristine or vinorelbine;

- anti-tumour nucleoside derivatives for example 5-fluorouracil, gemcitabine or capecitabine;
- alkylating agents such as nitrogen mustard or nitrosourea for example cyclophosphamide, chlorambucil, carmustine or lomustine;
- anti-tumour anthracycline derivatives for example daunorubicin, doxorubicin, idarubicin or mitoxantrone;
- HER2 antibodies for example trastuzumab;
- estrogen receptor antagonists or selective estrogen receptor modulators for example tamoxifen, toremifene, droloxifene, faslodex or raloxifene;
- aromatase inhibitors such as exemestane, anastrozole, letrazole and vorozole;
- differentiating agents such as retinoids, vitamin D and retinoic acid metabolism blocking agents (RAMBA) for example accutane;
- DNA methyl transferase inhibitors for example azacytidine;
- kinase inhibitors for example flavoperidol, imatinib mesylate or gefitinib;
- farnesyltransferase inhibitors;
- HDAC inhibitors;
- other inhibitors of the ubiquitin-proteasome pathway for example Velcade; or
- Yondelis.

The term "platinum coordination compound" is used herein to denote any tumour cell growth inhibiting platinum coordination compound which provides platinum in the form of an ion.

The term "taxane compounds" indicates a class of compounds having the taxane ring system and related to or derived from extracts from certain species of yew (Taxus) trees.

The term "topisomerase inhibitors" is used to indicate enzymes that are capable of altering DNA topology in eukaryotic cells. They are critical for important cellular functions and cell proliferation. There are two classes of topoisomerases in eukaryotic cells, namely type I and type II. Topoisomerase I is a monomeric enzyme of approximately 100,000 molecular weight. The enzyme binds to DNA and introduces a transient single-strand break, unwinds the double helix (or allows it to unwind) and subsequently reseals the break before dissociating from the DNA strand. Topisomerase II has a similar mechanism of action which involves the induction of DNA strand breaks or the formation of free radicals.

The term “camptothecin compounds” is used to indicate compounds that are related to or derived from the parent camptothecin compound which is a water-insoluble alkaloid derived from the Chinese tree Camptothecin acuminata and the Indian tree Nothapodytes foetida.

The term “podophyllotoxin compounds” is used to indicate compounds that are related to or derived from the parent podophyllotoxin, which is extracted from the mandrake plant.

The term “anti-tumour vinca alkaloids” is used to indicate compounds that are related to or derived from extracts of the periwinkle plant (Vinca rosea).

The term “alkylating agents” encompass a diverse group of chemicals that have the common feature that they have the capacity to contribute, under physiological conditions, alkyl groups to biologically vital macromolecules such as DNA. With most of the more important agents such as the nitrogen mustards and the nitrosoureas, the active alkylating moieties are generated *in vivo* after complex degradative reactions, some of which are enzymatic. The most important pharmacological actions of the alkylating agents are those that disturb the fundamental mechanisms concerned with cell proliferation in particular DNA synthesis and cell division. The capacity of alkylating agents to interfere with DNA function and integrity in rapidly proliferating tissues provides the basis for their therapeutic applications and for many of their toxic properties.

The term “anti-tumour anthracycline derivatives” comprise antibiotics obtained from the fungus *Strep. peuticus var. caesius* and their derivatives, characterised by having a tetracycline ring structure with an unusual sugar, daunosamine, attached by a glycosidic linkage.

Amplification of the human epidermal growth factor receptor 2 protein (HER 2) in primary breast carcinomas has been shown to correlate with a poor clinical prognosis for certain patients. Trastuzumab is a highly purified recombinant DNA-derived humanized monoclonal IgG1 kappa antibody that binds with high affiniity and specificity to the extracellular domain of the HER2 receptor.

Many breast cancers have estrogen receptors and growth of these tumours can be stimulated by estrogen. The terms “estrogen receptor antagonists” and “selective estrogen receptor modulators” are used to indicate competitive inhibitors of estradiol

binding to the estrogen receptor (ER). Selective estrogen receptor modulators, when bound to the ER, induces a change in the three-dimensional shape of the receptor, modulating its binding to the estrogen responsive element (ERE) on DNA.

In postmenopausal women, the principal source of circulating estrogen is from conversion of adrenal and ovarian androgens (androstenedione and testosterone) to estrogens (estrone and estradiol) by the aromatase enzyme in peripheral tissues. Estrogen deprivation through aromatase inhibition or inactivation is an effective and selective treatment for some postmenopausal patients with hormone-dependent breast cancer.

The term "antiestrogen agent" is used herein to include not only estrogen receptor antagonists and selective estrogen receptor modulators but also aromatase inhibitors as discussed above.

The term "differentiating agents" encompass compounds that can, in various ways, inhibit cell proliferation and induce differentiation. Vitamin D and retinoids are known to play a major role in regulating growth and differentiation of a wide variety of normal and malignant cell types. Retinoic acid metabolism blocking agents (RAMBA's) increase the levels of endogenous retinoic acids by inhibiting the cytochrome P450-mediated catabolism of retinoic acids.

DNA methylation changes are among the most common abnormalities in human neoplasia. Hypermethylation within the promotors of selected genes is usually associated with inactivation of the involved genes. The term "DNA methyl transferase inhibitors" is used to indicate compounds that act through pharmacological inhibition of DNA methyl transferase and reactivation of tumour suppressor gene expression.

The term "kinase inhibitors" comprises potent inhibitors of kinases that are involved in cell signalling, cell cycle progression and programmed cell death (apoptosis).

The term "farnesyltransferase inhibitors" is used to indicate compounds that were designed to prevent farnesylation of Ras and other intracellular proteins. They have been shown to have effect on malignant cell proliferation and survival.

The term "histone deacetylase inhibitor" or "inhibitor of histone deacetylase" is used to identify a compound, which is capable of interacting with a histone deacetylase and inhibiting its activity, more particularly its enzymatic activity. Inhibiting histone

deacetylase enzymatic activity means reducing the ability of a histone deacetylase to remove an acetyl group from a histone.

The term "other inhibitors of the ubiquitin-proteasome pathway" is used to indentify compounds that inhibit the targeted destruction of cellular proteins in the proteasome, including cell cycle regulatory proteins.

In view of their useful pharmacological properties, the components of the combinations according to the invention, i.e. the other medicinal agent and a cell cycle specific kinase inhibitor of formula (I) may be formulated into various pharmaceutical forms for administration purposes. The components may be formulated separately in individual pharmaceutical compositions or in a unitary pharmaceutical composition containing both components.

The present invention therefore also relates to a pharmaceutical composition comprising the other medicinal agent and a cell cycle specific kinase inhibitor of formula (I) together with one or more pharmaceutical carriers.

The present invention further relates to the use of a combination according to the invention in the manufacture of a pharmaceutical composition for inhibiting a proliferative disorder and/or a differentiative disorder.

The present invention further relates to a product containing as first active ingredient a cell cycle specific kinase inhibitor of formula (I) and as second active ingredient another medicinal agent, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from a proliferative disorder and/or a differentiative disorder.

The other medicinal agent and a cell cycle specific kinase inhibitor of formula (I) may be administered simultaneously (e.g. in separate or unitary compositions) or sequentially in either order. In the latter case, the two compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is achieved. It will be appreciated that the preferred method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend on the particular other medicinal agent and the cell cycle specific kinase inhibitor of formula (I) being administered, their route of administration, the particular proliferative disorder and/or differentiative disorder being treated and the particular host being treated. The optimum method and order of

administration and the dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the information set out herein.

The platinum coordination compound is advantageously administered in a dosage of 1 to 500mg per square meter (mg/m^2) of body surface area, for example 50 to 400 mg/m^2, particularly for cisplatin in a dosage of about 75 mg/m^2 and for carboplatin in about 300mg/m^2 per course of treatment.

The taxane compound is advantageously administered in a dosage of 50 to 400 mg per square meter (mg/m^2) of body surface area, for example 75 to 250 mg/m^2, particularly for paclitaxel in a dosage of about 175 to 250 mg/m^2 and for docetaxel in about 75 to 150 mg/m^2 per course of treatment.

The camptothecin compound is advantageously administered in a dosage of 0.1 to 400 mg per square meter (mg/m^2) of body surface area, for example 1 to 300 mg/m^2, particularly for irinotecan in a dosage of about 100 to 350 mg/m^2 and for topotecan in about 1 to 2 mg/m^2 per course of treatment.

The anti-tumour podophyllotoxin derivative is advantageously administered in a dosage of 30 to 300 mg per square meter (mg/m^2) of body surface area, for example 50 to 250mg/m^2, particularly for etoposide in a dosage of about 35 to 100 mg/m^2 and for teniposide in about 50 to 250 mg/m^2 per course of treatment.

The anti-tumour vinca alkaloid is advantageously administered in a dosage of 2 to 30 mg per square meter (mg/m^2) of body surface area, particularly for vinblastine in a dosage of about 3 to 12 mg/m^2 , for vincristine in a dosage of about 1 to 2 mg/m^2 , and for vinorelbine in dosage of about 10 to 30 mg/m^2 per course of treatment.

The anti-tumour nucleoside derivative is advantageously administered in a dosage of 200 to 2500 mg per square meter (mg/m^2) of body surface area, for example 700 to1500 mg/m^2, particularly for 5-FU in a dosage of 200 to 500mg/m^2, for gemcitabine in a dosage of about 800 to 1200 mg/m^2 and for capecitabine in about 1000 to 2500 mg/m^2 per course of treatment.

The alkylating agents such as nitrogen mustard or nitrosourea is advantageously administered in a dosage of 100 to 500 mg per square meter (mg/m^2) of body surface area, for example 120 to 200 mg/m^2, particularly for cyclophosphamide in a dosage of

about 100 to 500 mg/m^2 , for chlorambucil in a dosage of about 0.1 to 0.2 mg/kg, for carmustine in a dosage of about 150 to 200 mg/m^2 , and for lomustine in a dosage of about 100 to 150 mg/m^2 per course of treatment.

The anti-tumour anthracycline derivative is advantageously administered in a dosage of 10 to 75 mg per square meter (mg/m^2) of body surface area, for example 15 to 60 mg/m^2, particularly for doxorubicin in a dosage of about 40 to 75 mg/m^2, for daunorubicin in a dosage of about 25 to 45mg/m^2 , and for idarubicin in a dosage of about 10 to 15 mg/m^2 per course of treatment.

Trastuzumab is advantageously administered in a dosage of 1 to 5 mg per square meter (mg/m^2) of body surface area, particularly 2 to 4mg/m^2 per course of treatment.

The antiestrogen agent is advantageously administered in a dosage of about 1 to 100mg daily depending on the particular agent and the condition being treated. Tamoxifen is advantageously administered orally in a dosage of 5 to 50 mg, preferably 10 to 20 mg twice a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Toremifene is advantageously administered orally in a dosage of about 60mg once a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Anastrozole is advantageously administered orally in a dosage of about 1mg once a day. Droloxifene is advantageously administered orally in a dosage of about 20-100mg once a day. Raloxifene is advantageously administered orally in a dosage of about 60mg once a day. Exemestane is advantageously administered orally in a dosage of about 25mg once a day.

These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7, 14, 21 or 28 days.

The compounds of formula (I), the acid addition salts and stereoisomeric forms thereof can have valuable diagnostic properties in that they can be used for detecting or identifying an a cell cycle specific kinase in a biological sample comprising detecting or measuring the formation of a complex between a labelled compound and/or CDK4, AURORA A and/or AURORA B and/or other molecules, peptides, proteins, enzymes or receptors.

The detecting or identifying methods can use compounds that are labelled with labelling agents such as radioisotopes, enzymes, fluorescent substances, luminous substances, etc. Examples of the radioisotopes include ^{125}I, ^{131}I, ^{3}H and ^{14}C. Enzymes

are usually made detectable by conjugation of an appropriate substrate which, in turn catalyses a detectable reaction. Examples thereof include, for example, beta-galactosidase, beta-glucosidase, alkaline phosphatase, peroxidase and malate dehydrogenase, preferably horseradish peroxidase. The luminous substances include, for example, luminol, luminol derivatives, luciferin, aequorin and luciferase. Biological samples can be defined as body tissue or body fluids. Examples of body fluids are cerebrospinal fluid, blood, plasma, serum, urine, sputum, saliva and the like.

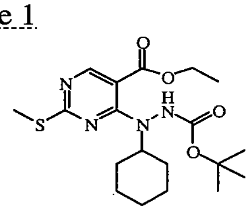
Experimental part

Hereinafter, the term 'THF' means tetrahydrofuran, 'EtOH' means ethanol, 'DMSO' means dimethylsulfoxide, 'DCM' means dichloromethane, 'DIPE' means diisopropyl ether, 'EtOAc' means ethyl acetate, 'Et_2O' means diethyl ether,'HBTU' means 1-[bis(dimethylamino)methylene]- 1*H*-benzotriazolium,, hexafluorophosphate(1-), 3-oxide,'HOBt' means 1-hydroxy- 1*H*-benzotriazole , '$LiAlH_4$' means lithiumaluminiumhydride, 'MeOH' means methanol, 'mcPBA' means 3-chlorobenzenecarboperoxoic acid. 'TEA' means triethylamine and 'TFA' means trifluoroacetic acid.

A. Preparation of the intermediate compounds

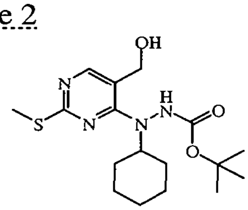
Example A1

a) Preparation of intermediate 1



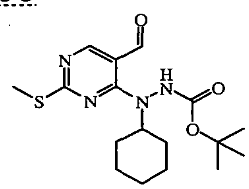
TEA (0.159 mol) was added at room temperature to a mixture of 4-chloro-2-(methylthio)-5-pyrimidinecarboxylic acid ethyl ester (0.0534 mol) and 2-cyclohexylhydrazinecarboxylic acid 1,1-dimethylethyl ester (0.1068 mol) in THF (125 ml). The mixture was stirred at room temperature overnight. The solvent was evaporated. The residue was taken up in DCM. The organic layer was washed with satured $NaHCO_3$, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 37.2 g (>100%) of intermediate 1.

b) Preparation of intermediate 2



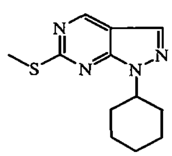
A solution of intermediate 1 (0.0633 mol) in THF (200 ml) was added dropwise at room temperature to a suspension of $LiAlH_4$ (0.1014 mol) in THF (200 ml). The mixture was stirred at room temperature for 3 hours. EtOAc was added dropwise. Then water (6 ml) was added. The mixture was filtered over celite. Celite was washed with EtOAc. The filtrate was evaporated. The residue (23 g) was purified by column chromatography over silica gel (35-70μm) (eluent: DCM/MeOH/NH_4OH 96/4/0.5). The desired fractions were collected and the solvent was evaporated, yielding 2.2 g (9 %) of intermediate 2.

c) Preparation of intermediate 3



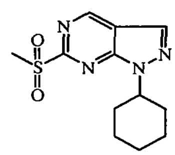
Manganese dioxide (2.7 g) was added at room temperature to a mixture of intermediate 2 (0.0057 mol) in DCM (100ml). The mixture was stirred at room temperature for 24 hours. MnO_2 (1g) was added. The mixture was stirred for 24 hours, then filtered over celite. The filtrate was evaporated, yielding: 2.2 g (>100%) of intermediate 3.

d) Preparation of intermediate 4



HCl/2-propanol (2.2 ml) was added at room temperature to a mixture of intermediate 3 (0.006 mol) in EtOH (20 ml). The mixture was stirred at room temperature for 5 hours. The solvent was evaporated. The residue was taken up into ice water. The aqueous layer was basified with K_2CO_3. The mixture was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 1.3 g (88 %) of intermediate 4.

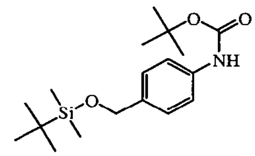
e) Preparation of intermediate 5



mcPBA 70% (0.0104 mol) was added at room temperature to a mixture of intermediate 4 (0.0052 mol) in DCM (30 ml). The mixture was stirred at room temperature overnight. K_2CO_3 10% was added. The mixture was extracted with DCM. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated, yielding 1.35 g (90%) of intermediate 5.

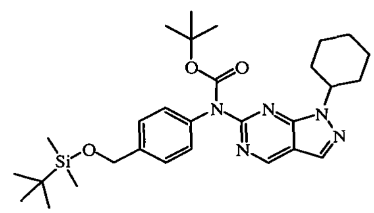
Example A2

a) Preparation of intermediate 6



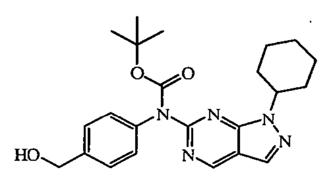
In a 100-ml two-neck reaction flask, 4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]- benzenamine (0.01662 mol) was dissolved in THF dry (25 ml). The solution was heated to 60°C on an oil-bath. A solution of dicarbonic acid, bis(1,1-dimethylethyl) ester (0.02078 mol) in THF dry (15 ml) was added dropwise and the reaction mixture was stirred for ± 4 hours. The solvent was evaporated. The residue (6.378 g) was purified by column chromatography over silica gel (eluent: EtOAc/hexane 5/95), then repurified by column chromatography over silica gel (eluent: DCM/hexane 1/1, then 6/4, then 7/3, ending with 100% DCM). The product fractions were collected and the solvent was evaporated, yielding 3.625 g (65%) of intermediate 6.

b) Preparation of intermediate 7



Intermediate 6 (0.00892 mol) was kept for 15 min in vacuo, then Argon was let in. Reaction was done under Argon. Intermediate 6 was dissolved in THF dry (15 ml) and the solution was cooled to 0°C (15 min). Ethylmagnesium chloride 2.8M/THF (0.00446 mol) was added dropwise and the mixture was stirred for 2 hours at 0°C to give solution I. Starting material intermediate 5 was kept for 15 min in vacuo, then Argon was let in. Intermediate 5 was dissolved in THF dry (15 ml) and this solution was added dropwise to the solution I. The reaction mixture was stirred until reaction was complete (ca. 40 minutes). The mixture was extracted with Et_2O/saturated aqueous $NaHCO_3$ solution/saturated aqueous NaCl solution. The separated organic layer was dried (Na_2SO_4), filtered and the solvent evaporated. The residue (3.350 g) was purified by column chromatography over silica gel (eluent: EtOAc/hexane 3/7). The product fractions were collected and the solvent was evaporated, yielding 0.921 g (96%) of intermediate 7.

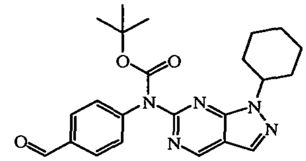
c) Preparation of intermediate 8



Intermediate 7 (0.000726 mol) was dissolved in THF dry (3 ml). A solution of tetrabutylammonium fluoride trihydrate (0.000871 mol) in THF dry (2 ml) was added

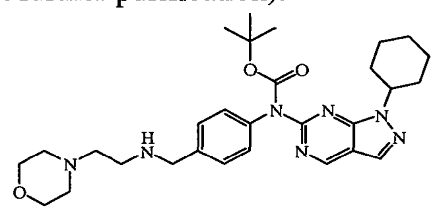
dropwise. The reaction mixture was stirred at room temperature for one hour. This mixture was extracted with Et_2O/water (2 x), then with an aqueous NaCl solution. The extract was filtered and the solvent was evaporated. The residue (0.400 g) was purified by column chromatography over silica gel (eluent: DCM/EtOAc/toluene 10/10/0.5). Two product fraction groups were collected. The purest fractions were combined and the solvent was evaporated, yielding 0.225 g (73%) of intermediate 8.

d) Preparation of intermediate 9



Manganese dioxide (0.011075 mol) was stirred in DCM (6 ml). The resulting suspension was stirred for 15 min at 0°C. A solution of intermediate 8 (0.000443 mol) in DCM (6 ml) was added dropwise and the reaction mixture was stirred for 2.5 hours at 0°C. The mixture was filtered over Na_2SO_4 and the filter cake was rinsed with DCM, then with EtOAc. The filtrate was evaporated, yielding 0.172 g of intermediate 9 (light foam, used in next reaction step, without further purification).

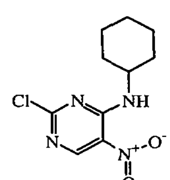
e) Preparation of intermediate 10



A solution of intermediate 9 (100 mg, 0.237 mmol) in dry THF (2 ml) was treated with 4-(2-aminoethyl)morpholine (62 ml, 0.475 mmol) and acetic acid (27 ml) and stirred at room temperature for 2 hours. After the addition of $NaBH(OAc)_3$ (151 mg, 0.712 mmol) stirring was continued for 27 hours. Normal workup (EtOAc, saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl solution, Na_2SO_4) and flash chromatography (DCM/MeOH 100:0 to 80:20), yielding 109 mg (85.7%) of intermediate 10.

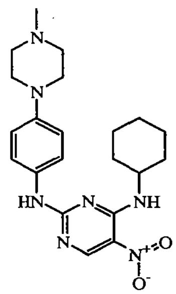
Example A3

a) Preparation of intermediate 11



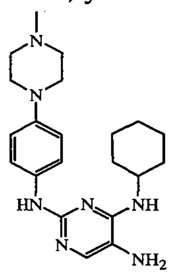
A solution of cyclohexanamine (0.062 mol) in *N,N*-dimethylacetamide (20 ml) was added dropwise to a cooled (-10°C) solution of 2,4-dichloro-5-nitropyrimidine (0.062 mol) and DIPE (8.1 g) in *N,N*-dimethylacetamide (80 ml), then the reaction mixture was allowed to reach room temperature overnight, yielding intermediate 11 (contains regio-isomer; used as such in the next reaction steps).

b) Preparation of intermediate 12



A mixture of intermediate 11 (0.031 mol), 4-(4-methyl-1-piperazinyl)- benzenamine, hydrochloride (0.031 mol) and DIPE (10 g) was heated at 60°C for 3 hours, then the reaction mixture was cooled and added dropwise to water (200 ml). The resulting solids were filtered off and dried in a vacuo at 60°C, yielding 9.6 g of intermediate 12.

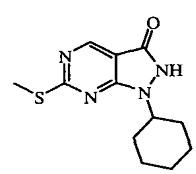
c) Preparation of intermediate 13



A mixture of intermediate 12 (0.023 mol) and TEA (10 ml) in THF (250 ml) was hydrogenated at 50°C with Pd/C 10% (2 g) as a catalyst in the presence of thiophene solution (1 ml). After uptake of H_2 (3 equiv.), the catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in DCM, washed with water and dried, yielding 6.7 g (76.5 %) of intermediate 13.

Example A4

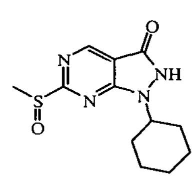
a) Preparation of intermediate 14



.HCl (1:1)

HCl/2-propanol (18ml) was added to a mixture of intermediate 1 (0.0292 mol) in EtOH (120ml). The mixture was stirred and refluxed for 3 hours and 30 minutes, then stirred at room temperature overnight. The solvent was evaporated. The residue was taken up in DIPE. The precipitate was filtered off and dried, yielding 6.5g of intermediate 14, isolated as a hydrochloric acid salt. This fraction was used directly in the next reaction step.

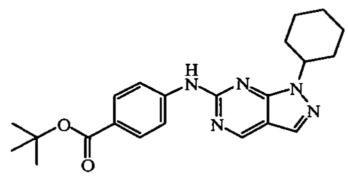
b) Preparation of intermediate 15



mcPBA 70% (0.0432 mol) was added portionwise at room temperature to a mixture of intermediate 14 (0.0216 mol) in DCM (80ml). The mixture was stirred at room temperature overnight. The mixture was purified by column chromatography over silica gel (70-200μm) (eluent: DCM/MeOH 95/5). The pure fractions were collected and the solvent was evaporated, yielding 2.2g (36%) of intermediate 15.

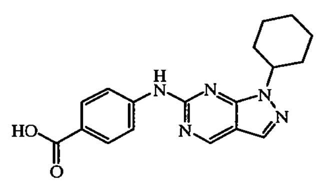
Example A5

a) Preparation of intermediate 16



Reaction in a sealed tube. A suspension of intermediate 5 (0.00178 mol), 4-aminobenzoic acid, 1,1-dimethylethyl ester (0.00267 mol) and cesium carbonate (0.00267 mol) in DMSO, abs. (5 ml) was stirred for 2 hours at 100°C. This mixture was extracted with EtOAc (3 x), water. The aqueous phase was treated with 1 N HCl until pH = 5. The acidic layer was re-extracted with EtOAc. The extract was washed with a saturated aqueous NaCl solution, then dried (Na_2SO_4), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: DCM/hexane 9/1, over 100% DCM, to hexane/EtOAc 1/1). The product fractions were collected and the solvent was evaporated, yielding 0.445 g (63.52%) of intermediate 16.

b) Preparation of intermediate 17

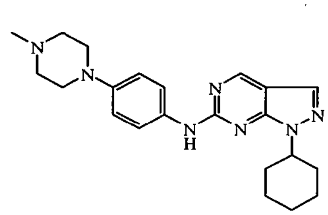


Intermediate 16 (0.001105 mol) was dissolved in DCM (10 ml). TFA(10 ml) was added dropwise via an addition funnel. The reaction mixture was stirred for one hour at room temperature. The solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator (2 x), yielding 0.564 g of intermediate 17.

B. Preparation of the final compounds

Example B1

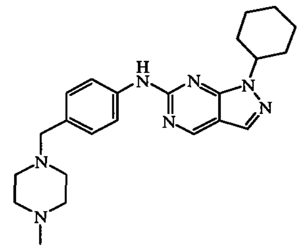
Preparation of compound 1



A mixture of intermediate 5 (0.0026 mol) and 4-(4-methyl-1-piperazinyl)-benzenamine (0.0107 mol) was stirred at 140°C for 1 hour, then brought to room temperature. DCM was added. The residue (3.3g) was purified by column chromatography over silica gel (15-35μm) (eluent: DCM/MeOH/NH_4OH 94/6/0.1). The pure fractions were collected and the solvent was evaporated. The residue (0.72g) was taken up in Et_2O. The precipitate was filtered off and dried, yielding 0.51g (49%) of compound 1, melting point: 180°C.

Example B2

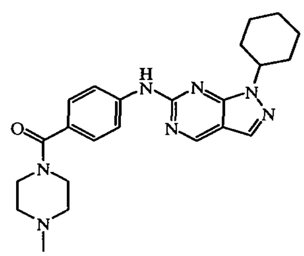
Preparation of compound 2



Reaction under Ar flow. Dry DMSO (0.25 ml) was added to intermediate 5 (0.000214 mol) and 4-[(4-methyl-1-piperazinyl)methyl]- benzenamine (0.000321 mol), under Argon. The reaction mixture was stirred for ± 20 hours at 100°C (oil-bath). This mixture was extracted with $CHCl_3$/2 x $NaHCO_3$/2 x water. The extract was filtered over silica gel ($MgSO_4$) and the solvent was evaporated. The residue (0.097 g) was purified by preperative HPLC (eluent: DCM/MeOH). The product fractions were collected and the solvent was evaporated, yielding 0.030 g (oil) of compound 2.

Example B3

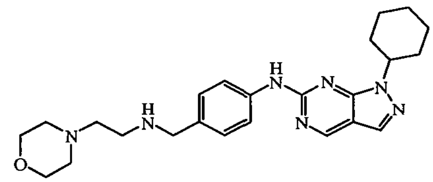
Preparation of compound 3



Reaction under Ar flow. Dry DMSO (1.5 ml) was added to a mixture of intermediate 5 (0.000428 mol), 1-(4-aminobenzoyl)-4-methyl- piperazine (0.000642 mol) and cesium carbonate (0.000642 mol). The reaction mixture was stirred for 3 hours at 100°C. This mixture was extracted with a mixture of EtOAc/$NaHCO_3$/H_2O/NaCl. The extract's solvent was evaporated. The residue (0.145 g) was purified by column chromatography over silica gel (eluent: DCM/MeOH gradient). The product fractions were collected and the solvent was evaporated, yielding 0.094 g of compound 3.

Example B4

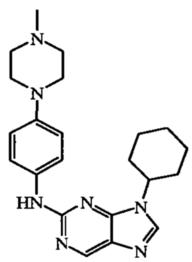
Preparation of compound 4



TFA (1.5 ml) was added to a solution of intermediate 10 (103 mg, 0.192 mmol) in dry DCM (1.5 ml). The solution was stirred at room temperature for 60 minutes followed by a normal workup (EtOAc, saturated aqueous $NaHCO_3$ solution, saturated aqueous NaCl solution,Na_2SO_4) and flash chromatography (DCM/MeOH 100:0 to 70:30), yielding 73 mg (87%) of compound 4 as colorless foam.

Example B5

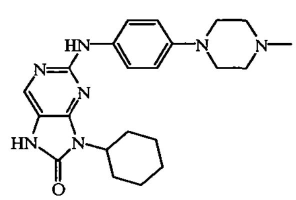
Preparation of compound 5



A mixture of intermediate 13 (0.00102 mol) and Gold's reagent (0.00144 mol) in dioxane (10 ml) was stirred and refluxed overnight, then the solvent was evaporated and the residue was partitioned between DCM/water. The layers were separated and the aqueous layer was extracted with DCM. The organic layers were combined, dried ($MgSO_4$), filtered off and the solvent was evaporated. The residue (0.43 g) was purified by reversed phase high-performance liquid chromatography. The pure fractions were collected and the solvent was evaporated. The residue was extracted with DCM (3 x 30 ml). The organic layer was dried ($MgSO_4$), filtered off and the solvent was evaporated, yielding 0.200 g of compound 5, melting point: 203.5-203.6°C.

Example B6

Preparation of compound 6

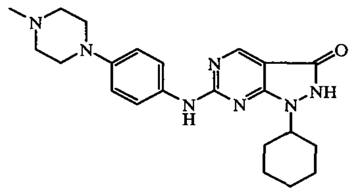


A mixture of intermediate 13 (0.00144 mol) and urea (0.002 mol) in xylene (50 ml) was stirred and refluxed for 16 hours. The solvent was evaporated and the residue was purified by reversed phase high-performance liquid chromatography. The product

fractions were collected and the solvent was evaporated, yielding 0.0767 g of compound 6, melting point: 294°C.

Example B7

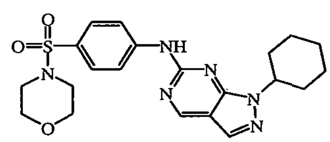
Preparation of compound 7



A mixture of intermediate 15 (0.0035 mol) and 4-(4-methyl-1-piperazinyl)-benzenamine (0.0142 mol) was stirred at 140°C for 2 hours, then brought to room temperature. DCM was added. The precipitate was filtered, washed several times with EtOH and dried with Et_2O, yielding 0.244g (17%) of compound 7, melting point: >260°C.

Example B8

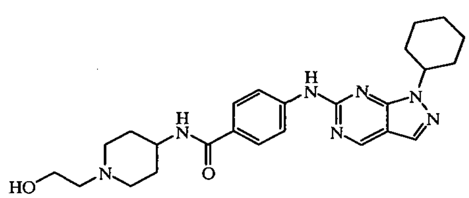
Preparation of compound 8



A mixture of intermediate 5 (80 mg, 0.285 mmol), 4-(morpholinosulfonyl)aniline (76 mg, 0.314 mmol) and cesium carbonate (102 mg, 0.314 mmol) was heated in dry DMSO (1 ml) to 100°C for 12 hours. Treatment of the mixture with EtOAc and saturated aqueous $NaHCO_3$ solution resulted in formation of a precipitate in the organic layer. The organic layer was separated, washed (water, saturated aqueous NaCl solution) and centrifuged. The pellet was washed (Et_2O/MeOH, Et_2O) and dried in vacuo, yielding 51 mg (40.5%) of compound 8, melting point 240°C.

Example B9

Preparation of compound 9

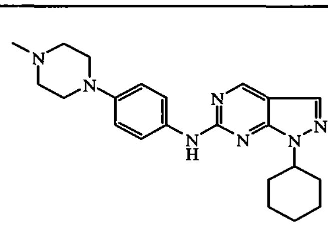
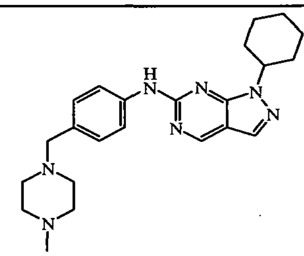


A suspension of intermediate 17 (0.000207 mol), 4-amino-1-piperidineethanol, dihydrochloride (0.000311 mol), HOBt (0.0003111 mol) and HBTU (0.0003111 mol) in DMF dry (1.5 ml) was stirred at room temperature. DIPE (0.001035 mol) was added and the reaction mixture was stirred overnight at room temperature. This mixture was extracted with Et_2O/aqueous $NaHCO_3$ solution, followed by water (2 x). The separated

organic layer was dried (Na_2SO_4), filtered and the solvent was evaporated. The residue (0.090 g) was purified by column chromatography over silica gel (eluent: DCM/MeOH 93/7, then 9/1; then eluent: DCM/(MeOH/NH_3 1%) 9/1; then: DCM/(MeOH/NH_3 2%) 9/1). The product fractions were collected and the solvent was evaporated, yielding 0.052 g of compound 9, melting point 177-181°C.

Table F-1 lists the compounds that were prepared according to the above described synthesis schemes.

<u>Table F-1</u>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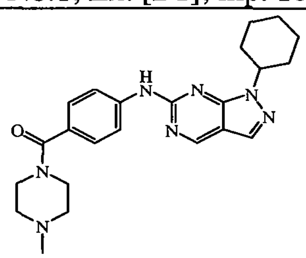	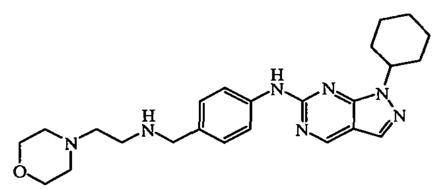
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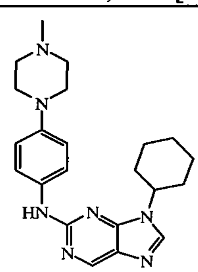	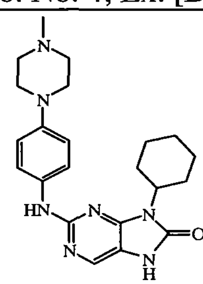
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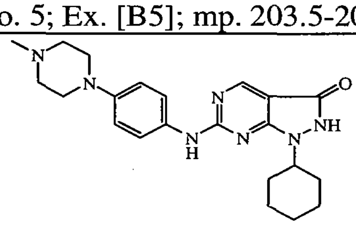	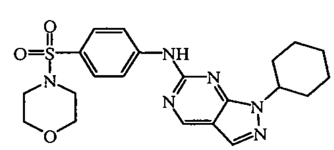
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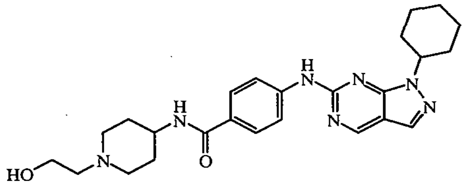
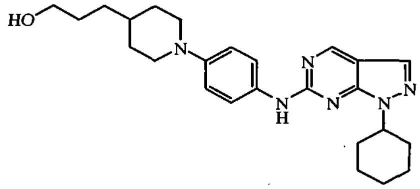
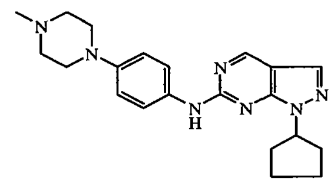
	
Co. No. 9; Ex. [B9]; mp. 177-181°C	
	
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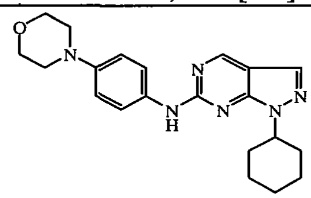	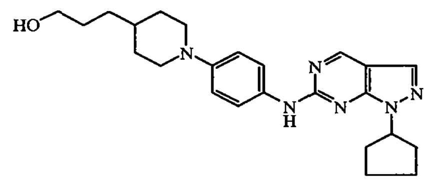
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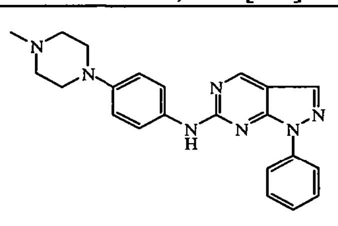	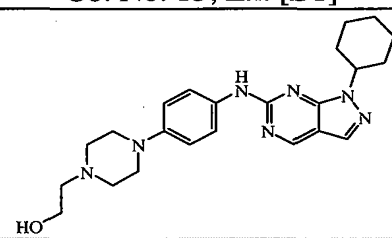
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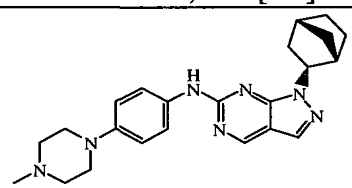	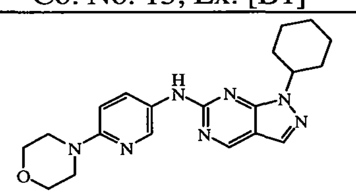
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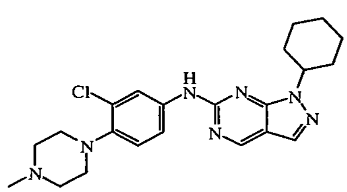	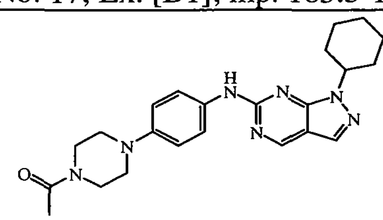
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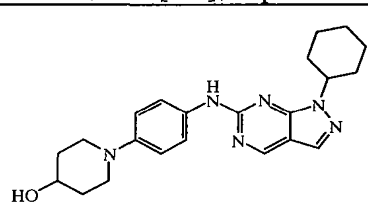	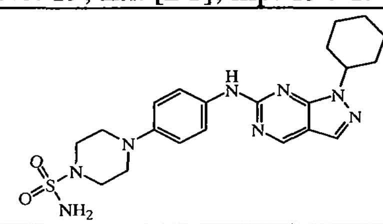
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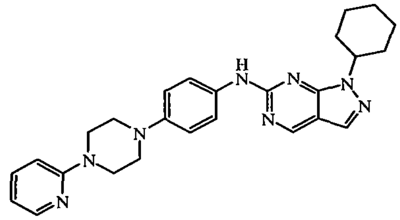	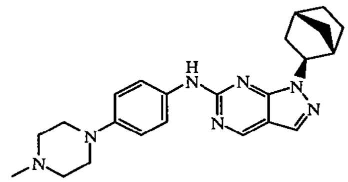
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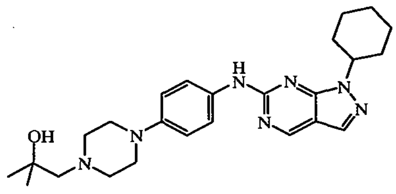	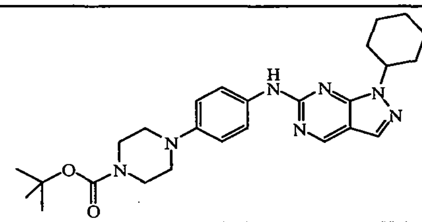
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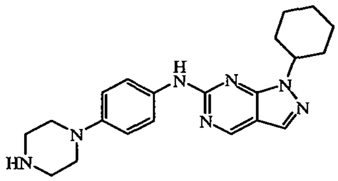
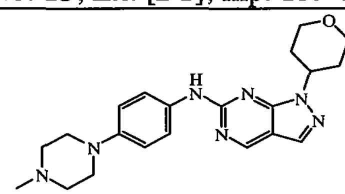
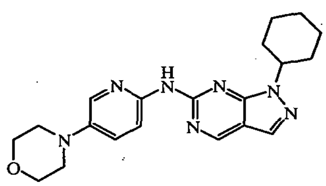
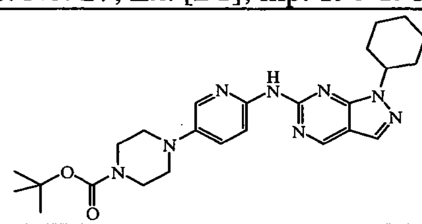
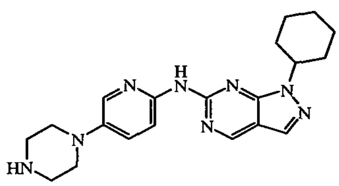
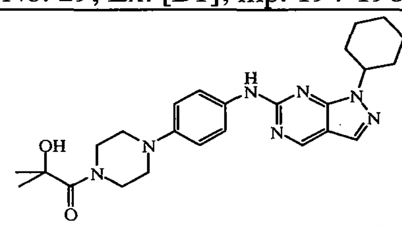
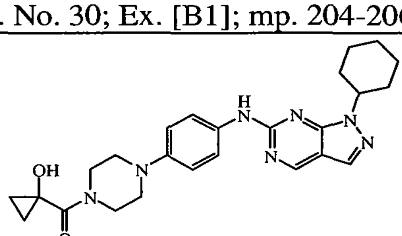
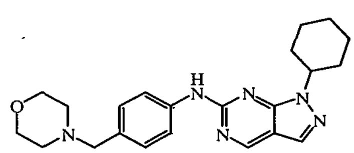
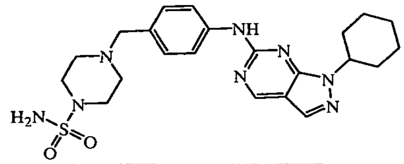
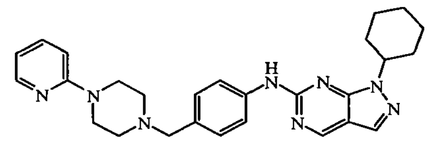
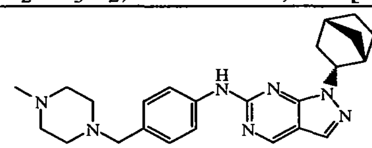
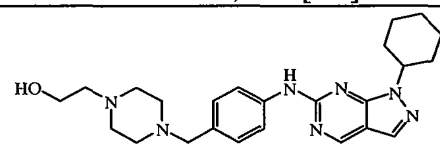
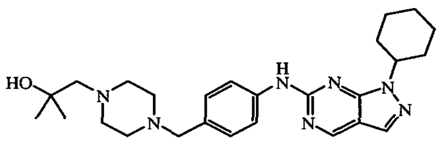
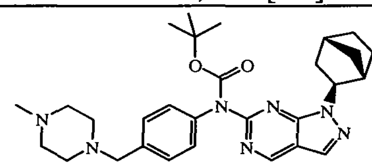
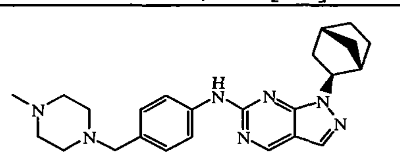
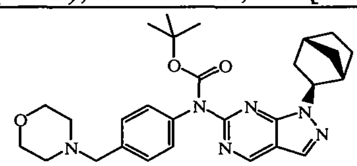
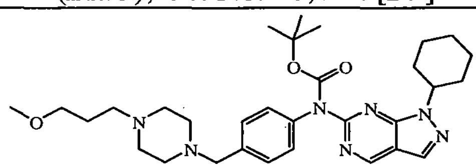
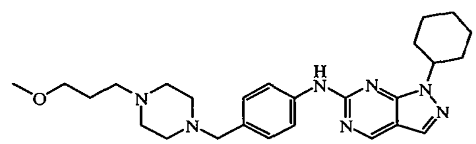
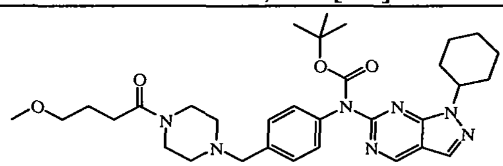
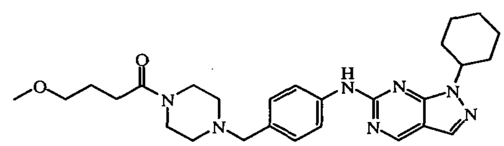
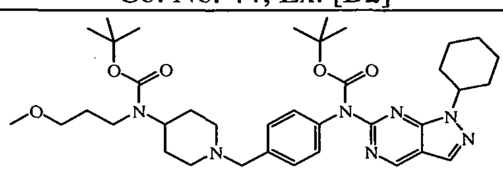
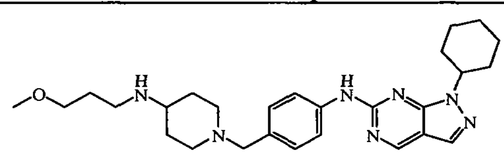
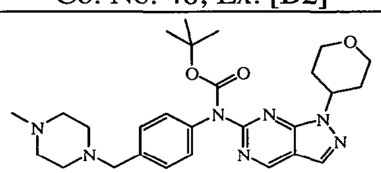
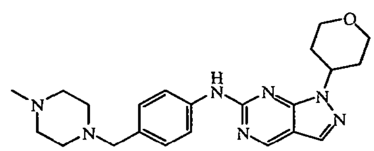
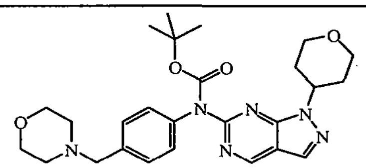
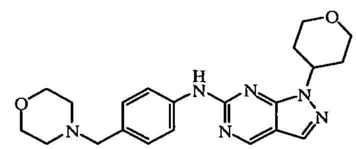
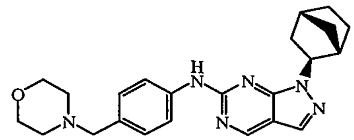
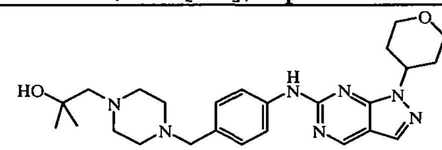
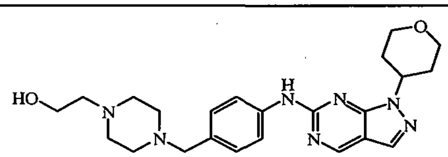
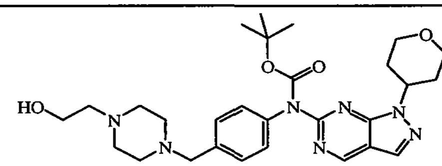
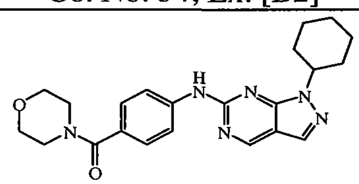
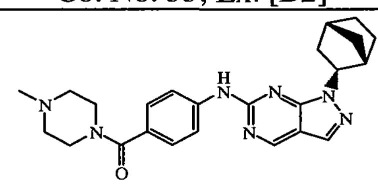
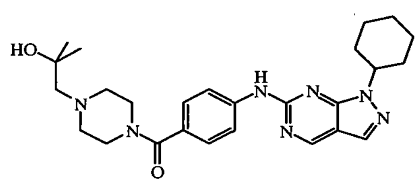
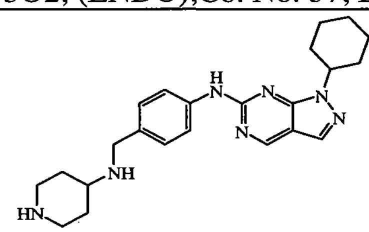
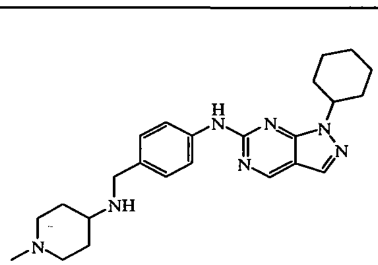
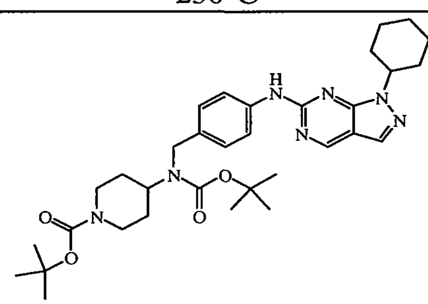
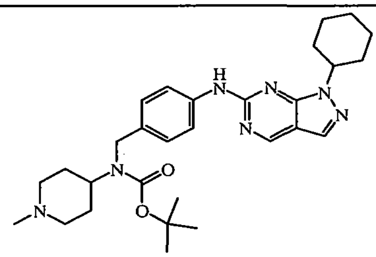
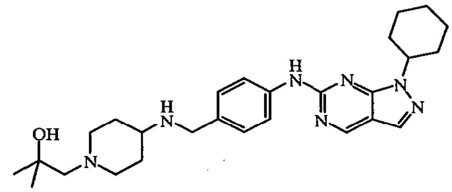
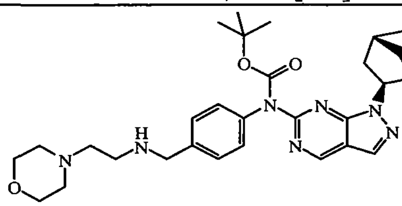
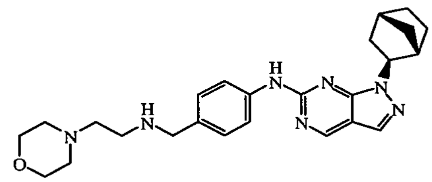
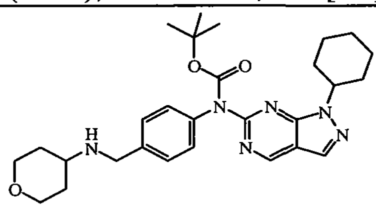
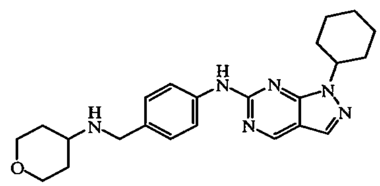
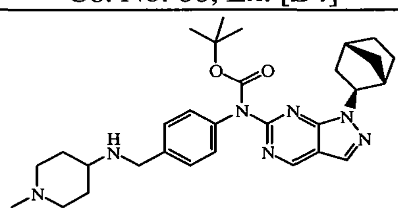
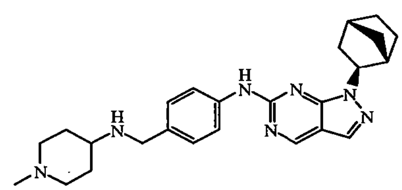
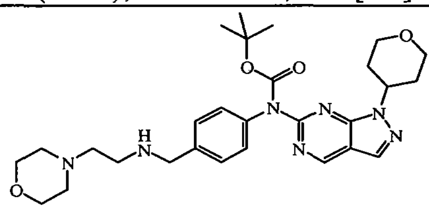
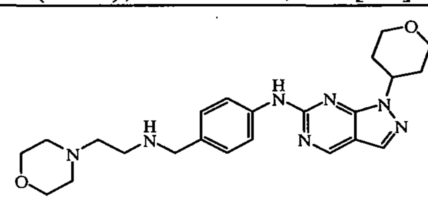
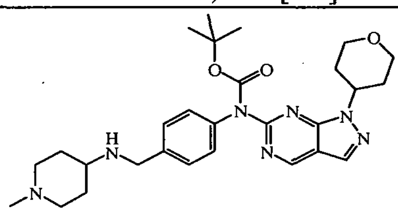
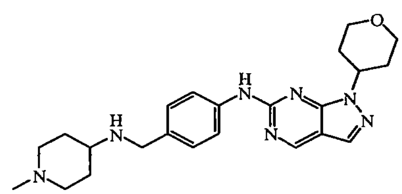
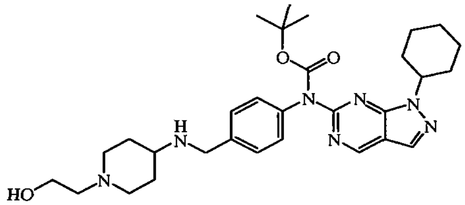
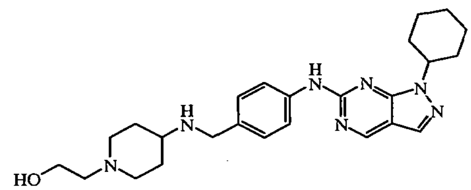
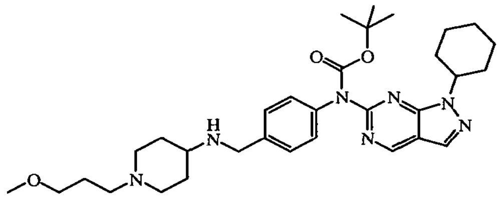
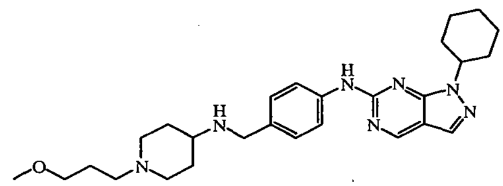
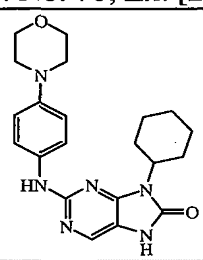
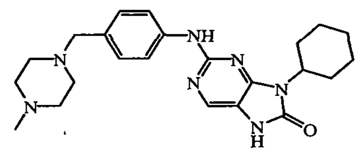
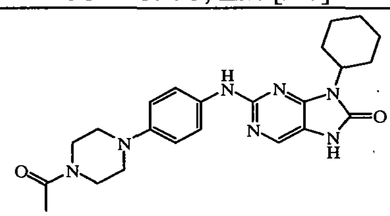
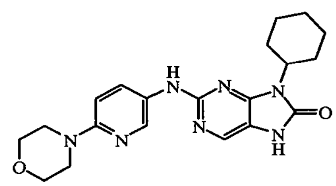
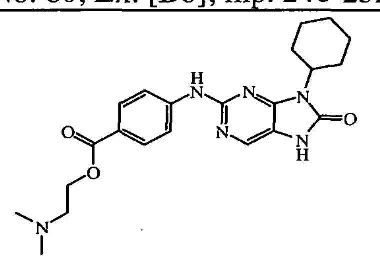
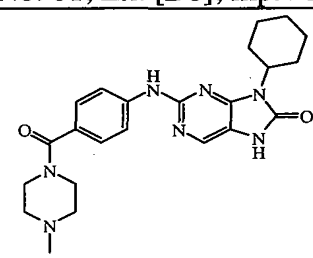
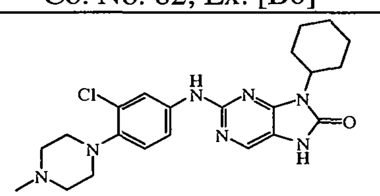
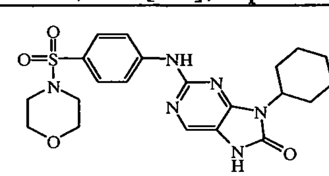
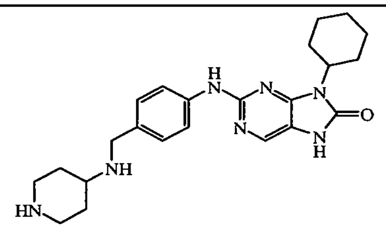
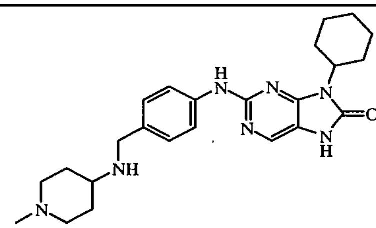
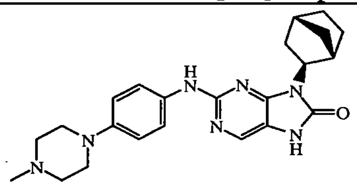
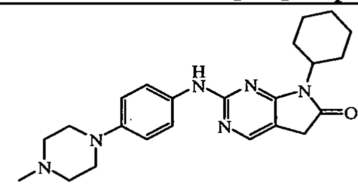
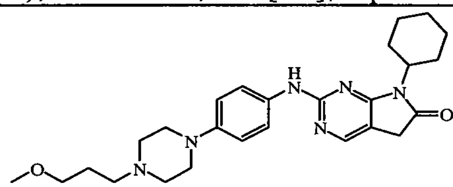
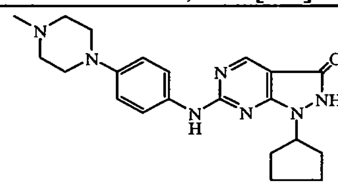
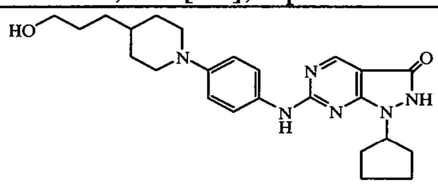
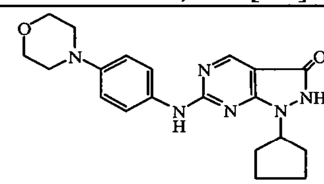
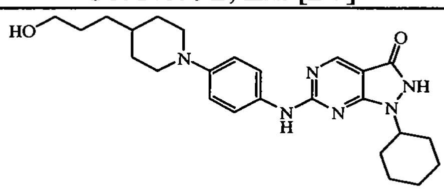
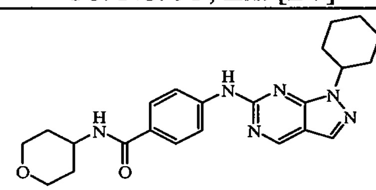
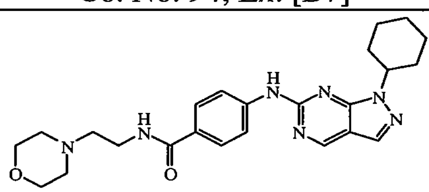
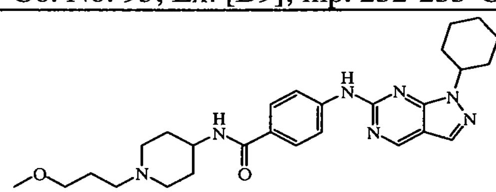
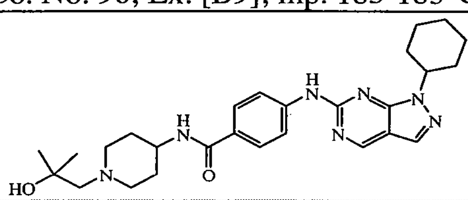
	
Co. No. 26; Ex. [B1]	Co. No. 27; Ex. [B1]; mp. 196-198°C
	
Co. No. 28; Ex. [B1]; mp. 228-230°C	Co. No. 29; Ex. [B1]; mp. 194-196.5°C
	
Co. No. 30; Ex. [B1]; mp. 204-206°C	Co. No. 31; Ex. [B1]
	
Co. No. 32; Ex. [B1]	Co. No. 33; Ex. [B2]; mp. 135-137°C

 $.C_2HF_3O_2$; Co. No. 34; Ex. [B2]	 Co. No. 35; Ex. [B2]
 (ENDO); Co. No. 36; Ex. [B2]	 Co. No. 37; Ex. [B2]
 Co. No. 38; Ex. [B2]	 (EXO); Co. No. 39; Ex. [B2]
 (EXO); Co. No. 40; Ex. [B2]	 (EXO); Co. No. 41; Ex. [B2]
 Co. No. 42; Ex. [B2]	 Co. No. 43; Ex. [B2]
 Co. No. 44; Ex. [B2]	 Co. No. 45; Ex. [B2]; mp. 134.5-137°C
 Co. No. 46; Ex. [B2]	 Co. No. 47; Ex. [B2]
 Co. No. 48; Ex. [B2]	 Co. No. 49; Ex. [B2]

	
Co. No. 50; Ex. [B2]	Co. No. 51; Ex. [B2]; mp. 161.5-165°C
	
(EXO); Co. No. 52; Ex. [B2]; mp. 161.5-164°C	Co. No. 53; Ex. [B2]
	
Co. No. 54; Ex. [B2]	Co. No. 55; Ex. [B2]
	
Co. No. 56; Ex. [B3]; mp. 207-208.5°C	.C2HF3O2; (ENDO);Co. No. 57; Ex. [B3]
	
Co. No. 58; Ex. [B3]	.2HCl; Co. No. 59; Ex. [B4]; mp. 249-250°C
	
.2HCl; Co. No. 60; Ex. [B4]; mp. 154-156°C	Co. No. 61; Ex. [B4]

	
Co. No. 62; Ex. [B4]	Co. No. 63; Ex. [B4]
	
(EXO); Co. No. 64; Ex. [B4]	(EXO); Co. No. 65; Ex. [B4]
	
Co. No. 66; Ex. [B4]	Co. No. 67; Ex. [B4]
	
(EXO); Co. No. 68; Ex. [B4]	(EXO); Co. No. 69; Ex. [B4]
	
Co. No. 70; Ex. [B4]	Co. No. 71; Ex. [B4]
	
Co. No. 72; Ex. [B4]	Co. No. 73; Ex. [B4]

	
Co. No. 74; Ex. [B4]	Co. No. 75; Ex. [B4]
	
Co. No. 76; Ex. [B4]	Co. No. 77; Ex. [B4]
	
Co. No. 78; Ex. [B6]	Co. No. 79; Ex. [B6]; mp. 230-232°C
	
Co. No. 80; Ex. [B6]; mp. 248-252°C	Co. No. 81; Ex. [B6]; mp. >250°C
	
Co. No. 82; Ex. [B6]	Co. No. 83; Ex. [B6]; mp. 240-243°C
	
Co. No. 84; Ex. [B6]; mp. 248-251°C	Co. No. 85; Ex. [B6]; mp. >250°C

 .2 HCl; Co. No. 86; Ex. [B6]; mp. >250°C	 .2 HCl; Co. No. 87; Ex. [B6]; mp. >250°C
 (EXO); Co. No. 88; Ex. [B6]; mp. >250°C	 Co. No. 89; Ex. [B6]
 Co. No. 90; Ex. [B6]; mp. 173-174°C	 Co. No. 91; Ex. [B7]
 Co. No. 92; Ex. [B7]	 Co. No. 93; Ex. [B7]
 Co. No. 94; Ex. [B7]	 Co. No. 95; Ex. [B9]; mp. 232-233°C
 Co. No. 96; Ex. [B9]; mp. 183-185°C	 Co. No. 97; Ex. [B9]; mp. >180°C (dec.)
 Co. No. 98; Ex. [B9]; mp. 233-236°C	

C. Pharmacological Example

The pharmacological activity of the present compounds was examined using the following test.

C.1. *In vitro* filtration assay for CDK4 inhibitory activity

Compounds of the present invention were tested in an *in vitro* filtration assay assessing CDK4 activity by means of its pRb-phosphorylation activity using [^{33}P]-ATP as phosphor donor. The radioactive phosphorylated pRb is then captured on filtermats and the incorporated [^{33}P] quantitated using a phosphorage storage screen.

The CDK4 kinase reaction is performed at 25°C for 45 minutes in a 96-well microtiterplate. The 25 μl reaction volume contains 50 mM Hepes pH 7.5, 10 mM NaF, 10 mM $MgCl_2$, 1 mM Na_3VO_4, 1 μM unlabeled ATP, 1mM DTT, 0.5 μCi $AT^{33}P$, 0.76 μg/well GST-pRb, 50 ng CDK4/cyclinD1 / well and 0.2 % compound in 100 % DMSO.
The reaction is stopped by adding 5 μl of a 3% phosphoric acid solution. 10 μl of the reaction mixture is then spotted onto a Filtermat P30 filter (Wallac) and washed 3 times for 5 min. in 75 mM phosphoric acid and 1 time for 5 min. in methanol prior to drying and quantification on the Typhoon (Amersham) using a phosphorage storage screen.

C.2. *In vitro* filtration assay for AURORA A inhibitory activity

Compounds of the present invention were tested in an *in vitro* filtration assay assessing AURORA A activity by means of its substrate-phosphorylation activity using [^{33}P]-ATP as phosphor donor. The radioactive phosphorylated substrate is then captured on filtermats and the incorporated [^{33}P] quantitated using a phosphorage storage screen.

The Aurora-A kinase reaction is performed at 25°C for 40 minutes in a 96-well microtiterplate. The 25 μl reaction volume contains 12 mM MOPS pH 7, 0.4 mM EDTA, 0.002 % Brij35, 1 % glycerol, 0.02 % beta-mercapto-ethanol, 0.2 mg/ml BSA, 1 μM unlabeled ATP, 0.2 μCi [^{33}P]-ATP, 200 μM Kemptide , 3 ng Aurora A/ well and 0.2 % compound in 100 % DMSO.
The reaction is stopped by adding 5 μl of a 3% phosphoric acid solution. 10 μl of the reaction mixture is then spotted onto a Filtermat P30 filter (Wallac) and washed 3 times for 5 min. in 75 mM phosphoric acid and 1 time for 5 min. in methanol prior to drying and quantification on the Typhoon (Amersham) using a phosphorage storage screen.

C.3 *In vitro* filtration assay for AURORA B inhibitory activity

Compounds of the present invention were tested in an *in vitro* filtration assay assessing AURORA B activity by means of its substrate-phosphorylation activity using [^{33}P]-ATP as phosphor donor. The radioactive phosphorylated substrate is then captured on filtermats and the incorporated [^{33}P] quantitated using a phosphorage storage screen.

The Aurora-B kinase reaction is performed at 25°C for 40 minutes in a 96-well microtiterplate. The 25 μl reaction volume contains 60 mM Hepes pH 7.5, 3 mM $MgCl_2$, 3 mM $MnCl_2$, 3 μM Na_3VO_4, 50 μg/ml PEG20000, 1 μM unlabeled ATP, 1mM DTT, 0.2 μCi AT^{33}P, 0.25 μg/well peptide (C(LRRWSLG)x4),100 ng Aurora-B/well and 0.2 % compound in 100 % DMSO.

The reaction is stopped by adding 5 μl of a 3% phosphoric acid solution. 10 μl of the reaction mixture is then spotted onto a Filtermat P30 filter (Wallac) and washed 3 times for 5 min. in 75 mM phosphoric acid and 1 time for 5 min. in methanol prior to drying and quantification on the Typhoon (Amersham) using a phosphorage storage screen.

C.4. *In vitro* Scintillation Proximity Assay (SPA) for CDK4 inhibitory activity

Compounds of the present invention were tested in an *in vitro* assay based on SPA technology.

In principle, the assay relies upon the well established SPA technology for the detection of CDK4 phosphorylated proteins, i.e pRb. This phosphorylation is performed using CDK4/cyclinD1 enzyme complex and ^{33}P-ATP as phosphor donor.

The CDK4 SPA kinase reaction is performed at 25°C for 30 minutes in a 96-well microtiter plate. The 100 μl reaction volume contains 40 mM Hepes, 6 mM NaF, 6 mM $MgCl_2$, 0.6 mM Na_3VO_4, 2 μg/ml Pepstatin, 2 μg/ml Leupeptin, 2 μg/ml Aprotinin, 50 μg/ml TLCK, 150 μg/ml DTT, 0.3 μg/ml benzamide, 0.1 μCi ^{33}P-ATP, 1.7 μg GST-pRb , 50 ng CDK4/cyclinD1 / well and 0.2 % compound in 100 % DMSO.

The reaction is stopped by adding to each well 100 μl of the glutathione coated SPA beads (10 mg/ml in PBS + 10 mM EDTA + 100 μM ATP + 0.05 % Triton X 100). The plates are then shaked at 300 rpm for 30 min to allow binding of the GST-tagged substrate to the glutathione coated beads. The beads are allowed to settle at the bottom of the plate for 30 minutes. The microtiterplates are centrifuges at 800 rpm for 10 minutes and the amount of phosphorylated (^{33}P) substrate is determined by counting (30sec/well) in a microtiterplate scintillation counter.

C.5. Calculation of pIC_{50} values

For each experiment, controls (containing enzyme (complex) and DMSO without compound), a blank incubation (containing DMSO but no enzyme (complex) or compound) and samples (containing enzyme (complex) and compound dissolved in DMSO) were run in parallel. All compounds tested were dissolved and eventually further diluted in DMSO. In first instance, compounds were tested at a concentration of 10^{-5} M. When the compounds showed activity at 10^{-5} M, a dose-response curve was made wherein the compounds were tested at concentrations between 10^{-5}M and 10^{-8}M. In each test, the blank value was subtracted from both the control and the sample values. The control sample represented maximal enzyme activity. For each sample, the amount of cpm was expressed as a percentage of the mean cpm value of the controls. When appropriate, IC_{50}-values (concentration of the drug, needed to reduce the enzyme activity to 50% of the control) were computed using linear interpolation between the experimental points just above and below the 50 % level. Herein the effects of test compounds are expressed as pIC_{50} (the negative log value of the IC_{50}-value). The inhibitory activity of the tested compounds of the invention is shown in Table-2

Table F-2: Table F-2 lists the results of the compounds that were tested according to example C.1, C.2, C.3 and C.4

Co. No.	cdk4 SPA see C.4	cdk4 filter see C.1	Aurora A see C.2	Aurora B see C.3
1	8.3	8.5	6.9	6.6
2		8.5	6.3	<5.0
3		8.2	6.3	<5.0
4		8.6	6.0	<5.8
5	5.5	6.2	<5.0	<5.0
6	7.0	6.6	<5.0	<5.0
7	6.8	7.1		6.4
8		7.0	6.3	<5.0
9		6.9	6.6	6.1
10	7.9	7.1	7.3	<5.0
11	8.2	7.5	6.8	6.4
12	7.7	7.4	7.2	6.6
13	7.3	7.2	7.3	<5.0
14	8.4	7.7	7.1	6.1
15		8.0	6.2	<5.0
16		7.5	6.4	<5.0
17		7.7	6.1	<5.0
18		6.6	6.8	<5.0
19		5.3	<5.0	<5.0
20		7.9	6.3	<5.0

Co. No.	cdk4 SPA see C.4	cdk4 filter see C.1	Aurora A see C.2	Aurora B see C.3
21		7.4	6.7	5.5
22		6.3	7.4	<5.0
23		8.3	7.0	6.8
24		6.9	6.6	5.5
25		6.0	7.0	5.5
26		7.8	6.6	5.9
27		6.7	6.3	<5.0
28		6.0	5.6	<5.0
29		5.2	<5.0	<5.0
30		7.3	<5.0	<5.0
31		7.5		
33		6.2	7.8	5.1
34		7.2	6.8	<5.0
35		7.0	6.6	<5.0
36		7.0	6.6	<5.0
37		8.1	6.7	6.4
38		7.9	6.0	5.7
39		5.8	5.2	<5.0
40		7.2	6.5	6.4
41		5.4	5.5	5.5
42		<5.0	<5.0	<5.0
43		7.2	6.9	5.4
44		<5.0	<5.0	<5.0
45		6.4	6.7	5.8
46		<5.0	<5.0	<5.0
47		7.5	6.5	5.4
48		<5.0	<5.0	<5.0
49		5.9	5.9	5.0
50		<5.0	<5.0	<5.0
51		5.3	6.0	<5.0
52		7.1	6.8	6.5
53		6.3	<5.0	5.1
54		6.2	<5.0	<5.0
55		<5.0	<5.0	<5.0
56		7.6	6.9	5.5
57		7.0	7.0	5.1
58		6.2	6.9	5.9
59		7.8	6.1	<5.0
60		8.1	5.8	<5.0
61		<5.0	5.9	<5.0
62		7.6	6.8	5.2
63		7.6	6.0	5.6
64		5.2	<5.0	<5.0
65		6.7	6.3	6.3
66		5.1	5.0	<5.0
67		6.6	5.8	6.0
68		6.0	5.2	5.1

Co. No.	cdk4 SPA see C.4	cdk4 filter see C.1	Aurora A see C.2	Aurora B see C.3
69		7.6	6.2	6.0
70		<5.0	<5.0	<5.0
71		5.6	5.3	<5.0
72		<5.0	<5.0	<5.0
73		6.2	<5.0	<5.0
75		6.9	5.8	5.9
76		<5.0	<5.0	<5.0
77		7.1	<5.0	5.7
78	6.2	6.0		
79		5.7	<5.0	<5.0
80		5.4	5.6	<5.0
81		5.3	<5.0	<5.0
82		5.7	<5.0	<5.0
83		5.6	<5.0	<5.0
84		6.2	5.2	<5.0
85		<5.0	5.5	<5.0
86		5.6	5.3	<5.0
87		5.4	<5.0	<5.0
88		5.7	5.8	<5.0
89		6.5	5.8	5.5
90		6.5	5.8	5.8
91	5.9	6.2	5.1	<5.0
92	5.6	5.2		<5.0
93	5.6	5.3	5.8	<5.0
94	6.0	5.8	5.5	<5.0
95		6.1	6.9	6.2
96		6.2	7.0	5.9
97		6.2	6.4	6.3
98		6.4	6.5	5.8

The compounds were further evaluated on *in vitro* assays measuring inhibition of different kinase activities, on cell lines and eventually in *in vivo* tests.

C.6. Analytical data

The mass of the compounds was recorded with LCMS (liquid chromatography mass spectrometry). The analytical HPLC (column: Develosil RPAq 4.6 x 50 mm) was performed with different gradient eluent systems at a flow rate of 1.5 ml/min with UV detection at 220 nm and 254 nm. Different eluent systems were used which are described below. The data are gathered in Table F-3 below.

System A: 5% acetonitrile, 95% water (0.1% trifluoro acetic acid)
to 100% acetonitrile in 5 min

System B: 10% acetonitrile, 90% water (0.1% trifluoro acetic acid) to 100% acetonitrile in 5 min

System C: 20% acetonitrile, 80% water (0.1% trifluoro acetic acid) to 100% acetonitrile in 5 min

System D: 30% acetonitrile, 70% water (0.1% trifluoro acetic acid) to 100% acetonitrile in 5 min

System E: 40% acetonitrile, 60% water (0.1% trifluoro acetic acid) to 100% acetonitrile in 5 min

System F: 50% acetonitrile, 50% water (0.1% trifluoro acetic acid) to 100% acetonitrile in 5 min

System G: 10% acetonitrile, 90% water (0.1% trifluoro acetic acid) to 30% acetonitrile, 70% water (0.1% trifluoro acetic acid) in 5 min

System H: 10% acetonitrile, 90% water (0.1% trifluoro acetic acid) to 40% acetonitrile, 60% water (0.1% trifluoro acetic acid) in 5 min

System I: 60% acetonitrile, 40% water (0.1% trifluoro acetic acid) to 100% acetonitrile in 5 min

System J: 80% acetonitrile, 20% water (0.1% trifluoro acetic acid) to 100% acetonitrile in 5 min

System K: 15% acetonitrile, 85% water (0.1% trifluoro acetic acid) to 100% acetonitrile in 5 min

System L: 70% acetonitrile, 30% water (0.1% trifluoro acetic acid) to 100% acetonitrile in 5 min

Table F-3: LCMS parent peak and retention time values.

Co. No.	Retention time (minutes)	LCMS [M+H]	Eluent System
1	3.23	392	K
2	3.45	406	A
3	3.41	420	B
4	3.44	436	A
6	3.13	408	A
8	3.67	443	D
9	3.26	464	K

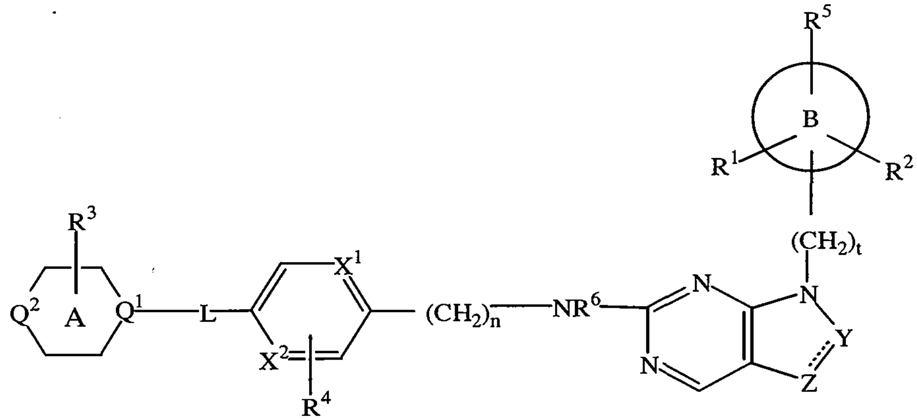
Co. No.	Retention time (minutes)	LCMS [M+H]	Eluent System
15	3.42	422	B
16	3.78	404	A
17	3.33	380	K
18	3.86	426	B
19	2.47	420	D
20	3.45	393	B
21	3.89	457	B
22	3.31	455	C
23	3.62	404	B
24	3.58	450	A
25	2.23	478	F
26	3.58	378	A
27	2.90	394	B
28	3.31	380	C
29	3.58	479	D
30	3.32	379	A
31	2.48	464	D
32	3.34	462	C
33	3.07	393	C
35	3.15	469	K
36	3.39	418	B
37	3.43	436	A
38	3.50	464	A
39	4.00	518	A
40	3.58	418	A
41	3.32	505	D
42	2.74	564	D
43	3.50	464	A
44	3.11	592	D
45	3.77	492	A
46	3.25	678	E
47	3.30	478	B
48	3.35	508	A
49	2.77	408	B
50	3.54	495	A

Co. No.	Retention time (minutes)	LCMS [M+H]	Eluent System
51	3.17	395	A
52	3.55	405	K
53	2.82	466	B
54	2.74	438	B
55	3.33	538	A
56	4.11	407	B
57	3.54	432	B
58	3.64	478	A
59	3.38	406	A
60	3.37	420	A
61	2.97	606	L
62	3.92	520	A
63	3.40	478	A
64	3.99	548	A
65	3.56	448	A
66	3.84	507	K
67	3.57	407	B
68	3.90	532	A
69	3.51	432	A
70	3.33	538	A
71	3.00	438	A
72	3.30	522	A
73	2.97	422	A
74	3.79	550	A
75	3.36	450	A
76	3.83	578	A
77	3.43	478	A
79	3.05	422	A
80	3.00	436	K
81	2.80	396	K
83	2.78	436	B
84	3.33	442	A
85	3.47	459	B
86	3.00	422	A
87	3.00	436	A

Co. No.	Retention time (minutes)	LCMS [M+H]	Eluent System
88	3.17	420	A
89	2.60	407	A
90	3.11	465	B
95	4.23	421	B
96	3.71	450	A
97	3.64	4.92	B
98	3.57	492	B

Claims

1. A compound of formula (I),



(I)

a *N*-oxide, an addition salt, a quaternary amine and a stereochemically isomeric form thereof, wherein

X^1 and X^2 are each independently N or CH with the exception that X^1 and X^2 can not be both N;

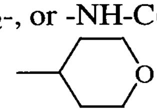
Q^1 is CH_2, or N;

Q^2 is CH_2, N, or O;

n is an integer with value 0 or 1 and when n is 0 then a direct bond is intended;

t is an integer with value 0 or 1 and when t is 0 then a direct bond is intended;

—Y⋯Z— is –CH=N-, –C(=O)-NH-, –N=CH-, –C(=O)-CH_2-, or -NH-C(=O)-;

ring B represents phenyl, cyclopentyl, cyclohexyl, narbonyl or  ;

L is a direct bond, -$(CH_2)_r$–NR^7-$(CH_2)_s$-, -$(CR^8{}_2)_r$-O-$(CH_2)_s$-, -C(=O)-, -$(CH_2)_r$-O-C(=O)-, -$(CH_2)_r$-NR^7-C(=O)-, -S(=O)$_2$-, -$(CH_2)_r$-NH-S(=O)$_2$-, or -C_{1-6}alkyl-; wherein

each -$(CH_2)_r$– moiety is linked to ring A;

each s is an integer with value 0 or 1 and when s is 0 then a direct bond is intended;

each r is an integer with value 0, 1, 2 or 3 and when r is 0 then a direct bond is intended;

each R^7 is hydrogen, C_{1-6}alkyl or C_{1-4}alkyloxycarbonyl;
each R^8 is independently hydrogen, hydroxy or C_{1-6}alkyl; or
two R^8 together can form a bivalent radical of formula $-CH_2-CH_2-$;

R^1, R^2 and R^5 are each independently hydrogen, hydroxy or C_{1-6}alkyl;

R^3 is hydrogen, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxycyclopropylC_{1-6}alkyl, hydroxycyclopropylcarbonyl,hydroxyC_{1-6}alkylcarbonyl, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxy, hydroxyC_{1-6}alkyloxyC_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-4}alkyloxycarbonyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxyC_{1-6}alkyl, pyridinyl, $-NR^9R^{10}$, or $-S(=O)_2-NR^9R^{10}$;
wherein each R^9 and R^{10} independently represent hydrogen, C_{1-6}alkyl, C_{1-4}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, hydroxycyclopropylC_{1-6}alkyl or C_{1-6}alkyloxyC_{1-6}alkyl;

R^4 is hydrogen or halo;

R^6 is hydrogen, C_{1-6}alkyl or C_{1-4}alkyloxycarbonyl.

2. A compound as claimed in claim 1 wherein X^1 and X^2 are each CH.

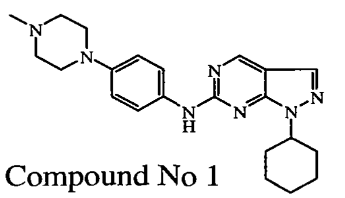
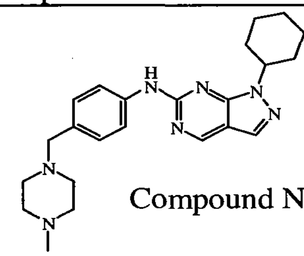
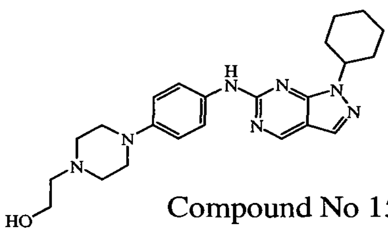
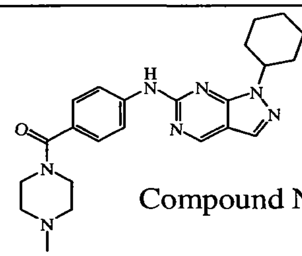
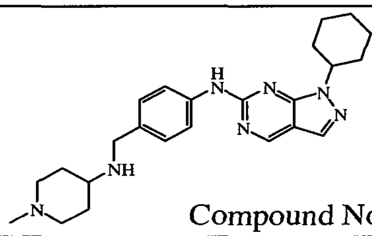
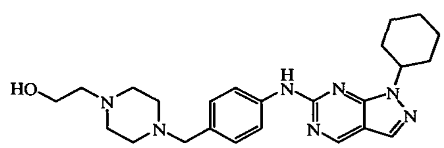
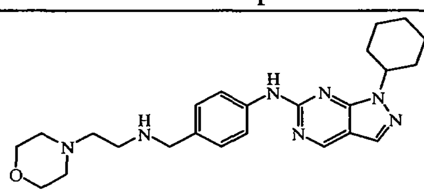
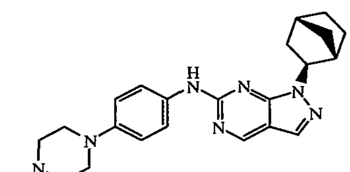
3. A compound as claimed in claim 1 or 2 wherein
n is 0; t is 0; L is a direct bond, $-(CH_2)_r-NR^7-(CH_2)_s-$, $-C(=O)-$, $-(CH_2)_r-NR^7-C(=O)-$, $-S(=O)_2-$ or $-C_{1-6}$alkyl-; s is 1; r is 0 or 2; each R^7 is hydrogen or C_{1-4}alkyloxycarbonyl; R^1, R^2 and R^5 are each independently hydrogen; R^3 is hydrogen, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxycyclopropylcarbonyl, hydroxyC_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyl, C_{1-4}alkyloxycarbonyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkylcarbonyl, pyridinyl, $-NR^9R^{10}$, or $-S(=O)_2-NR^9R^{10}$; each R^9 and R^{10} independently represent hydrogen, C_{1-4}alkyloxycarbonyl or C_{1-6}alkyloxyC_{1-6}alkyl; and R^6 is hydrogen or C_{1-4}alkyloxycarbonyl.

4. A compound as claimed in claim 1, 2 and 3 wherein
X^1 and X^2 are each CH; Q^2 is N, or O; n is 0; t is 0; $-Y{=}{=}{=}Z-$ is $-N{=}CH-$; ring B represents cyclohexyl or narbonyl; L is a direct bond, $-(CH_2)_r-NR^7-(CH_2)_s-$, $-C(=O)-$ or $-C_{1-6}$alkyl-; s is 1; r is 0 or 2; each R^7 is hydrogen; R^1, R^2 and R^5 are each independently hydrogen; R^3 is hydrogen,

C_{1-6}alkyl or hydroxyC_{1-6}alkyl; R^4 is hydrogen; and R^6 is hydrogen.

5. A compound as claimed in claim 1, 2, 3 and 4 wherein X^1 and X^2 are each CH; Q^2 is N, or O; n is 0; t is 0; $-Y{=}Z-$ is –N=CH-; ring B represents cyclohexyl or narbonyl; L is a direct bond, –NH-CH_2-, -C(=O)- or methyl; R^1, R^2 and R^5 are each independently hydrogen; R^4 is hydrogen; and R^6 is hydrogen.

6. A compound as claimed in claim 1, 2, 3, 4 and 5 wherein said compound is compound No 1, compound No 2, compound No 15, compound No 3, compound No 60, compound No 37, compound No 4 and compound No 23.

 Compound No 1	 Compound No 2
 Compound No 15	 Compound No 3
 Compound No 60	 Compound No 37
 Compound No 4	 Compound No 23

7. A pharmaceutical composition comprising pharmaceutically acceptable carriers and as an active ingredient a therapeutically effective amount of a compound as claimed in claim 1 to 6.

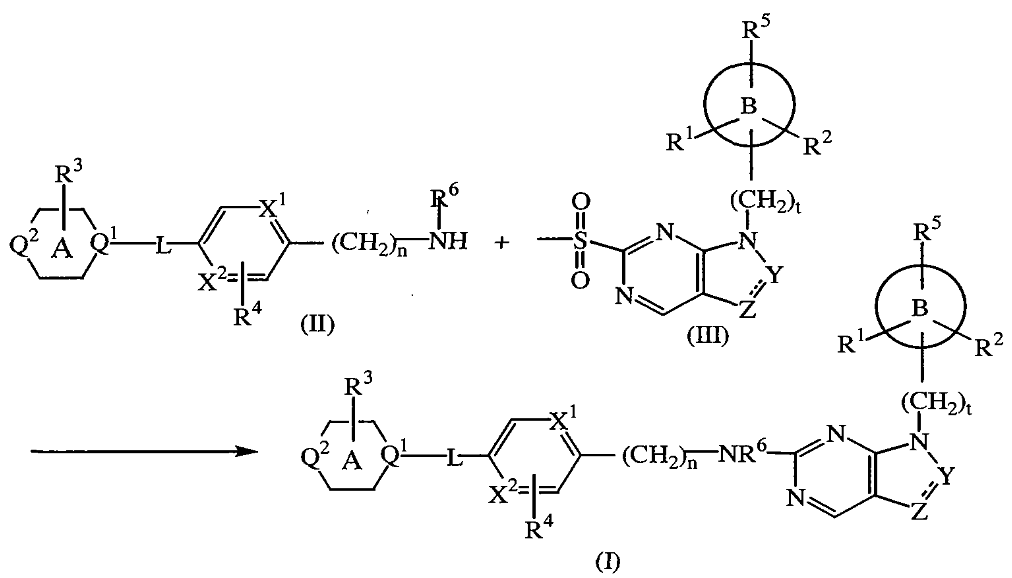
8. A process of preparing a pharmaceutical composition as claimed in claim 7 wherein the pharmaceutically acceptable carriers and a compound as claimed in claim 1 to 6 are intimately mixed.

9. A compound as claimed in any of claims 1 to 6 for use as a medicine.

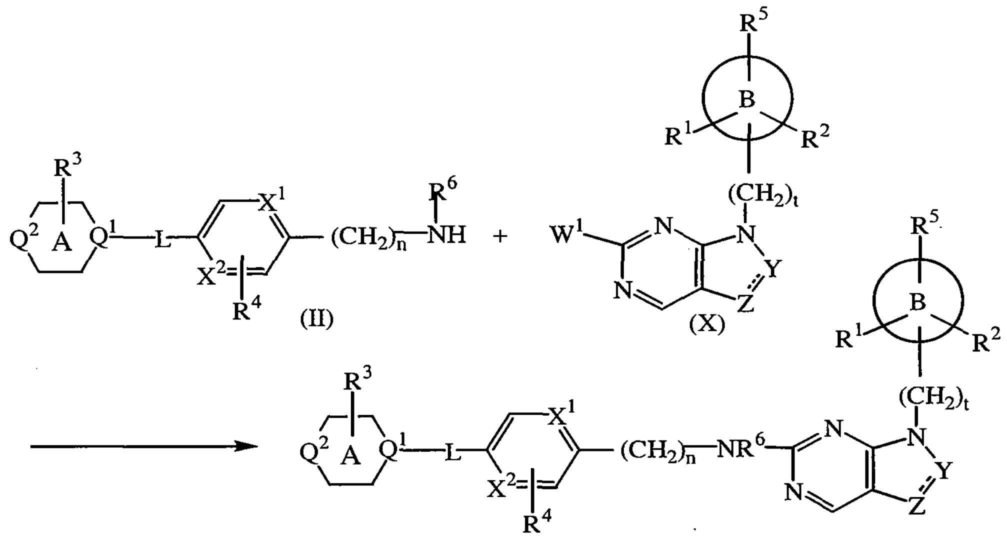
10. Use of a compound as claimed in any of claims 1 to 6 for the manufacture of a medicament for the treatment of proliferative diseases or differentiative disorders.

11. A combination of an anti-cancer agent and a cell cycle kinase inhibitor as claimed in any of claims 1 to 6.

12. A process for preparing a compound as claimed in claim 1, characterized by
   a) reacting an intermediate of formula (II) with an intermediate of formula (III) in the presence of a suitable solvent and optionally in the presence of a suitable base, resulting in a compound of formule (I),

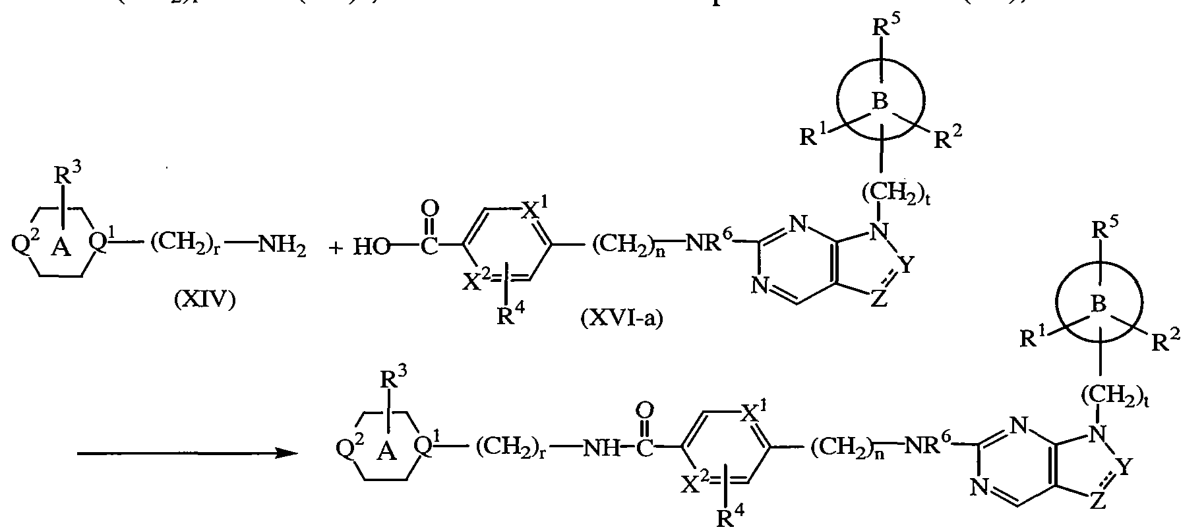


   b) reacting an intermediate of formula (X), wherein W^1 is a suitable leaving group, with an intermediate of formula (II) in the presence of a suitable solvent, optionally in the presence of a suitable base, resulting in the formation of a compound of formula (I),



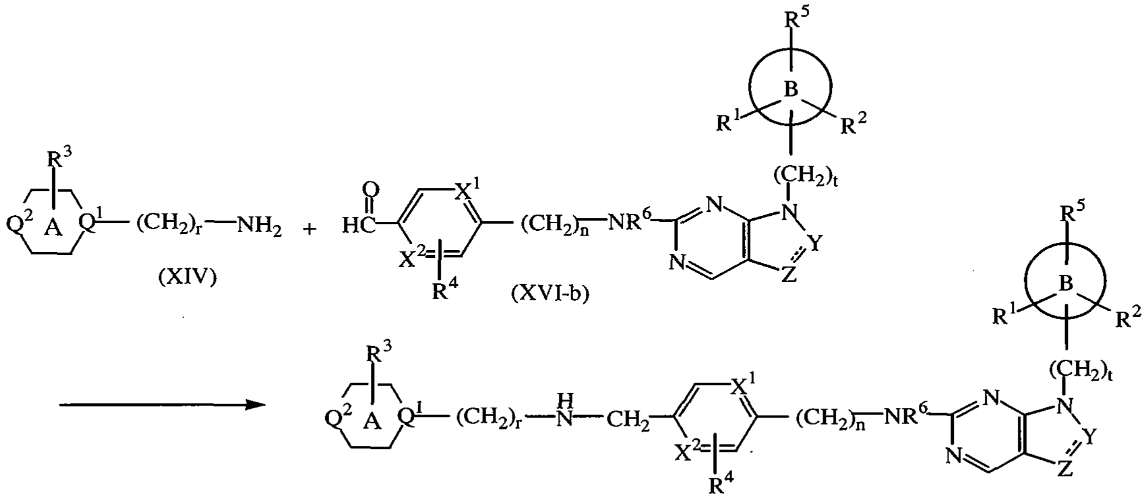
(I)

c) reacting an intermediate of formula (XIV) with an intermediate of formula (XVI-a) in the presence of a suitable solvent optionally in the presence of a suitable base with the formation of compounds of formula (I) wherein L is $-(CH_2)_r$-NH-C(=O)-, herein referred to as compounds of formula (I-a),



(I-a)

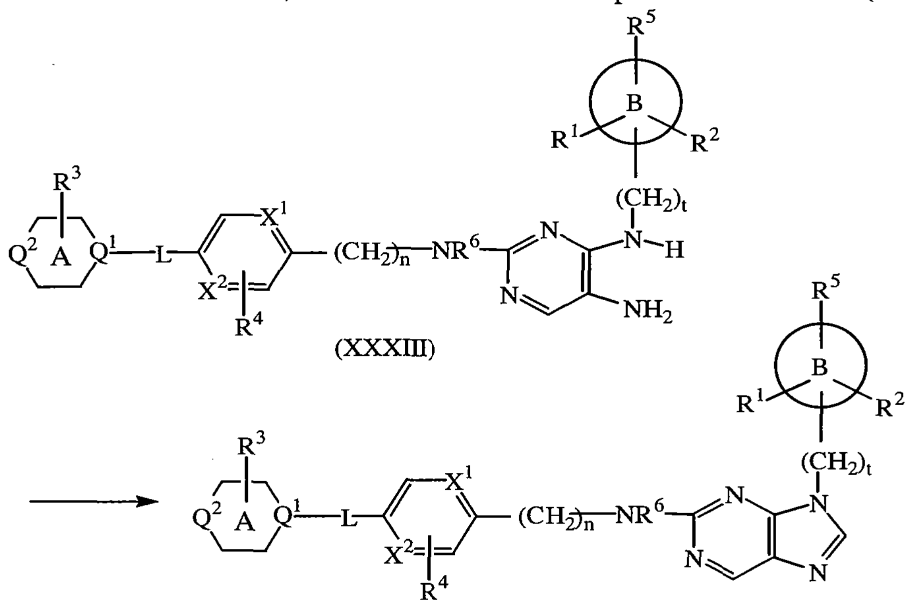
d) reacting intermediates of formula (XIV) with intermediates of formula (XVI-b) in the presence of sodium triacetoxyborohydride or sodium cyanoborohydride, in the presence of a suitable acid and in a suitable solvent, resulting in compounds of formula (I) wherein L is $-(CH_2)_r$-NH-(CH_2)-, herein referred to as compounds of formula (I-b),



(XIV) (XVI-b)

(I-b)

e) cyclizing an intermediate of formula (XXXIII) in the presence of a salt or an acid in a suitable solvent, resulting in compounds of formula (I), wherein —Y==Z— is –CH=N-, herein refered to as compounds of formula (I-c).



(XXXIII)

(I-c)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/050097

A. CLASSIFICATION OF SUBJECT MATTER
C07D473/32 C07D487/04 A61K31/519 A61K31/52 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/065378 A (WARNER-LAMBERT COMPANY LLC; BIWERSI, CATHLIN, MARIE; MCNAMARA, DENNIS,) 5 August 2004 (2004-08-05) examples 1,2,5-11,15,16	1-12
Y	WO 2004/094426 A (USTAV ORGANICKE CHEMIE A BIOCHEMIE AKADEMIE VED CESKE REPUBLIKY; HOCEK) 4 November 2004 (2004-11-04) page 44, line 30 - page 45, line 2; claim 1	1-12
Y	WO 01/49688 A (UNIVERSITAIRE INSTELLING ANTWERPEN; USTAV EXPERIMENTALNI BOTANIKY AKAD) 12 July 2001 (2001-07-12) claims 1,14	1-12

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 March 2006	03/04/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bakboord, J

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 147 108 A (USTAV EXPERIMENTALNI BOTANIKY AKADEMIE VED CESKE REPUBLIKY) 24 October 2001 (2001-10-24) cited in the application the examples	1-12
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/050097

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